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Blast Concussion mTBI, Hypopituitarism, and Psychological Health in OIF/OEF Veterans

PRINCIPAL INVESTIGATOR:

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CONTRACTING ORGANIZATION:

Seattle Institute for Biomedical and Clinical Research

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14. ABSTRACT

Studies of traumatic brain injury from all causes have found evidence of chronic posttraumatic hypopituitarism (PTHP) in 25–50% of cases. PTHP, and in particular adult growth hormone deficiency (GHD), is associated with symptoms resembling those of PTSD, including fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, cognitive deficiencies, and decreased quality of life. However, the prevalence of PTHP after blast related mild TBI (mTBI) has not previously been characterized. We have measured concentrations of 12 pituitary and target-organ hormones in two groups of male US Veterans of combat in Iraq or Afghanistan: one group with blast-related mTBI and a second group with similar deployment histories but without blast exposure. Our findings thus far are that 15 of 35, or 43% of the mTBI group were found to have one or more abnormal hormone levels. Seven Veterans in the mTBI group were found with hormone levels consistent with GHD, and five had testosterone and gonadotropin concentrations indicative of hypogonadism. One of the Veterans in the deployment control group was found to meet criteria for both GHD and hypogonadism. If symptoms characteristic of both PTHP and PTSD can be linked to neuroendocrine dysfunction, they may be amenable to treatment with hormone replacement. Hormonal evaluations of additional participants in both groups are in progress.

15. SUBJECT TERMS
traumatic brain injury, hypopituitarism, blast, concussion, growth hormone, testosterone

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INTRODUCTION:

Chronic hypopituitarism (deficient production of one or more anterior pituitary hormones) occurs in 25-50% of cases of civilian traumatic brain injury (TBI). However, the prevalence of posttraumatic hypopituitarism (PTHP) after blast concussion mild TBI (mTBI) has not been determined despite the fact that repetitive blast concussion is the signature injury of combat in Iraq and Afghanistan. PTHP is associated with symptoms easily mistaken for those of PTSD including fatigue, mood disturbances, anxiety and depression, irritability, insomnia, memory loss, social isolation, and decreased quality of life. Muscular weakness, erectile dysfunction, infertility, and diminished cardiovascular function are also frequent consequences. These symptoms, if appropriately diagnosed as consequences of PTHP, can be treated successfully with hormone replacement. The objectives of this study are to measure basal hormone concentrations in blood from Veterans who sustained at least one blast-induced concussion during deployment to Iraq or Afghanistan. The values will be compared to hormone levels in combat-zone Veterans without blast exposure or PTSD as well as civilian control subjects to determine the frequency and nature of pituitary dysfunction resulting from blast mTBI. Methods for screening for PTHP will be developed and refined. Accurate, routine diagnosis of PTHP has the potential of markedly improving the psychological health and facilitating the recovery of blast mTBI victims.

BODY:

Year One Research Accomplishments

Tasks 1-5 of the Statement of Work for this project were completed for 26 of the target goal of 40 participant samples from the mTBI group and for seven of the target goal of 20 participant samples for the deployment control group. The results of this work were fully described and published in the appended publication in *Frontiers in Neurology* (Appendix 1): Wilkinson CW, Pagulayan KF, Petrie EC, Mayer CL, Colasurdo EA, Shofer JB, Hart KL, Hoff D, Tarabochia MA, Peskind ER.
High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury. Front Neurol. 2012;3:11. doi: 10.3389/fneur.2012.00011. Epub 2012 Feb 7. (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3273706/?tool=pubmed) The abstract of the paper and six graphs and descriptive text that were not included in the publication follow.

Abstract:

Studies of traumatic brain injury from impact have found evidence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones at least one year after injury, in 25–50% of cases. Most studies found the occurrence of PTHP to be unrelated to injury severity. Growth hormone deficiency (GHD) and hypogonadism were reported most frequently. Hypopituitarism, and in particular adult GHD, is associated with symptoms that resemble those of PTSD, including fatigue, anxiety,

depression, irritability, insomnia, sexual dysfunction, cognitive deficiencies, and decreased quality of life. However, the prevalence of PTHP after blast-related mild TBI (mTBI), an extremely common injury in modern military operations, has not been characterized. We measured concentrations of 12 pituitary and target-organ hormones in two groups of male US Veterans of combat in Iraq or Afghanistan. One group consisted of participants with blast-related mTBI whose last blast exposure was at least one year prior to the study. The other consisted of Veterans with similar military deployment histories but without blast exposure. Eleven of 26, or 42% of participants with blast concussions were found to have abnormal hormone levels in one or more pituitary axes, a prevalence similar to that found after other forms of TBI. Five members of the mTBI group were found with markedly low age-adjusted insulin-like growth factor-I (IGF-I) levels indicative of probable GHD, and three had testosterone and gonadotropin concentrations consistent with hypogonadism. If symptoms characteristic of both PTHP and PTSD can be linked to pituitary dysfunction, they may be amenable to treatment with hormone replacement. Routine screening for chronic hypopituitarism after blast concussion shows promise for appropriately directing diagnostic and therapeutic decisions that otherwise may remain unconsidered and for markedly facilitating recovery and rehabilitation.

The graphs below depicting the prevalence of abnormalities of three pituitary hormones found in Veterans who had sustained blast mTBI were not included in the *Frontiers in Neurology* paper, and the data are described and interpreted in greater detail here than in the published manuscript. The three abnormalities are prolactin excess or deficiency, vasopressin excess or deficiency, and oxytocin deficiency.

Prolactin Excess/Deficiency:

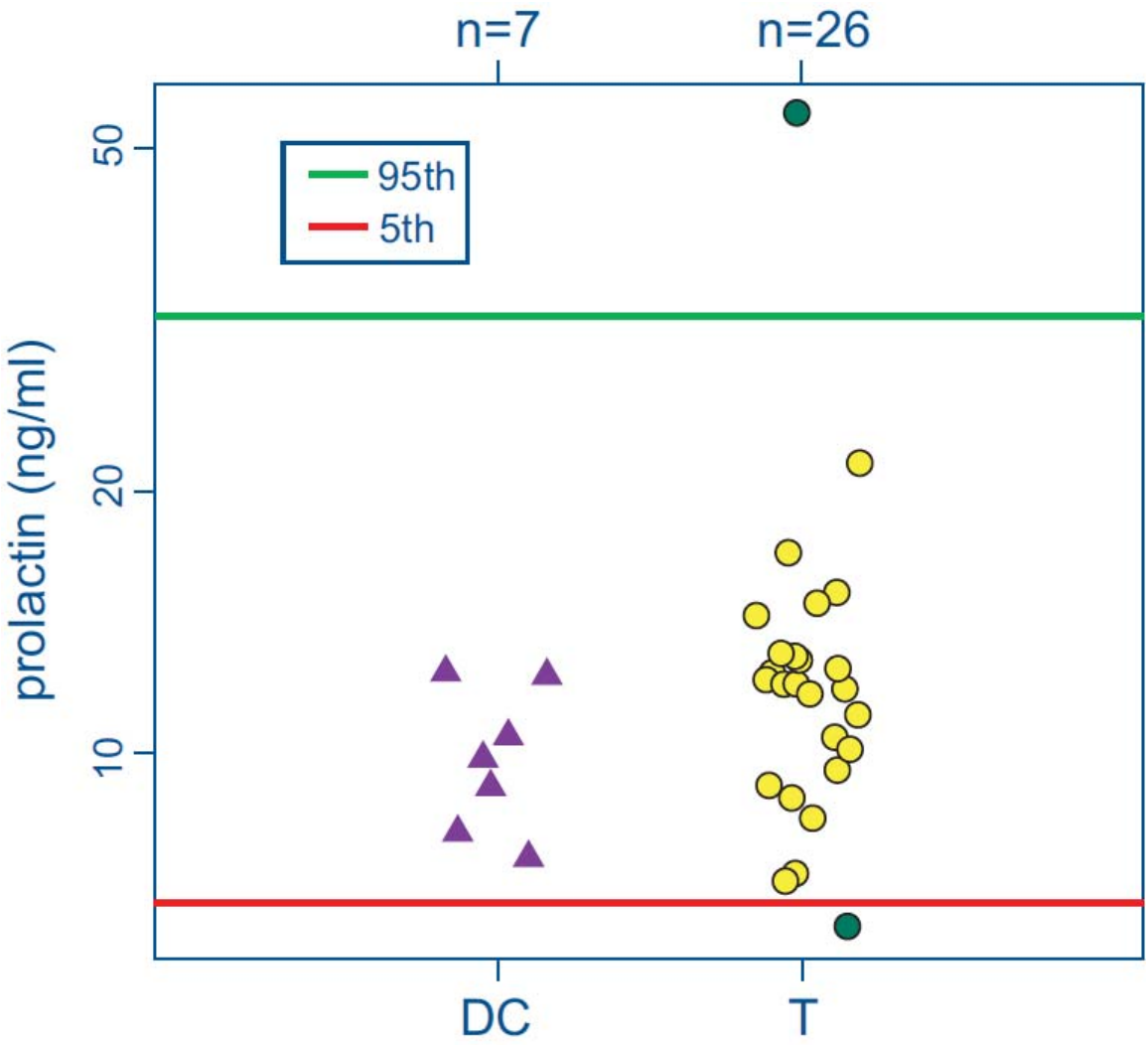

Figure 1. Both hypoprolactinemia and hyperprolactinemia are associated with sexual and reproductive dysfunction including erectile dysfunction and infertility. Data from the deployment control (DC) group are indicated on the left by purple triangles, and mTBI group data are shown by yellow circles on the right. Serum prolactin levels above the 95th percentile of the distribution of prolactin concentrations in our community control reference group were considered to be aberrant and indicative of hyperprolactinemia. Similarly, values below the 5th percentile of the distribution of prolactin concentrations in our reference sample were considered to be markers of hypoprolactinemia. None of the Veterans in the DC group were found with abnormal prolactin levels. However, one participant in the mTBI group had a prolactin value considered to abnormally low and one had an excessively high prolactin level. Data from these two Veterans are indicated by the green circles. The same two participants were also found to have probable hypogonadism as determined by our criteria based upon luteinizing hormone and testosterone concentrations (see *Frontiers in Neurology* publication in Appendix 1).

Vasopressin Excess/Deficiency:

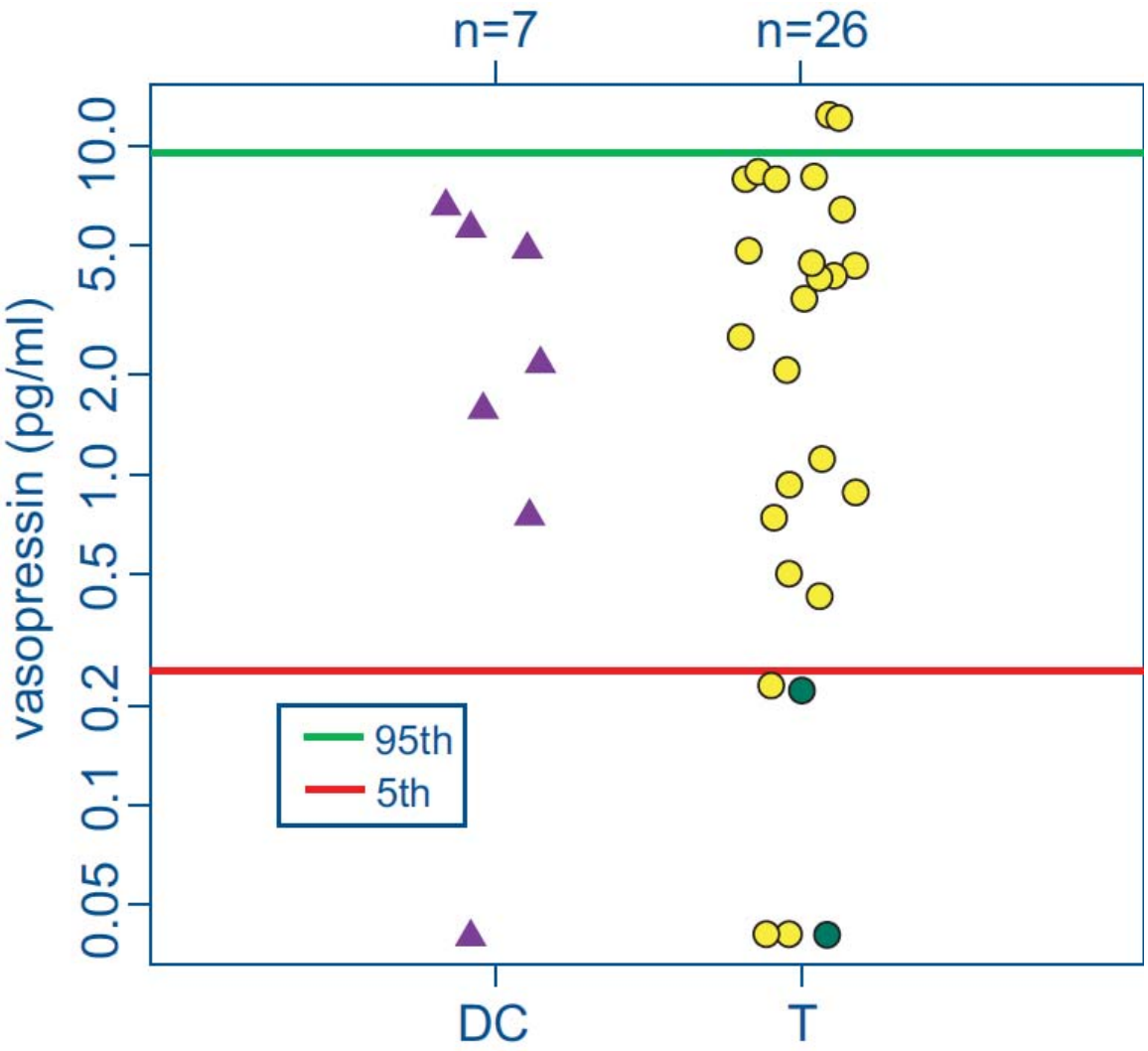

Figure 2. Similarly to the case with prolactin, both abnormally low and abnormally high levels of plasma vasopressin (antidiuretic hormone) are associated with serious medical conditions. Low levels (diabetes insipidus, DI) result in excessive thirst, excretion of large amounts of severely diluted urine, and potential dehydration. Abnormally high concentrations (syndrome of inappropriate antidiuretic hormone hypersecretion, SIADH) result in water retention and excess excretion of sodium. Elevated vasopressin concentrations in animals and humans have been linked to anxiety, depression, and aggression, and high plasma and/or CSF levels have been associated with personality disorder, depression, obsessive-compulsive disorder, schizophrenia, and PTSD. Data for each of the two subject groups are presented as in Figure 1. Our criterion for excessive vasopressin concentration was a level above the 95th percentile of our reference sample. Functional vasopressin deficiency was defined as a vasopressin concentration below the 5th percentile together with very dilute urine (urine specific gravity less than 1.003). Two of the mTBI group met our criterion for excessive vasopressin secretion, and two of the same group, indicated by the green circles, met both criteria for functional vasopressin deficiency (low vasopressin together

with severely diluted urine). None of the deployment control group was found to have abnormal plasma prolactin levels.

Oxytocin:

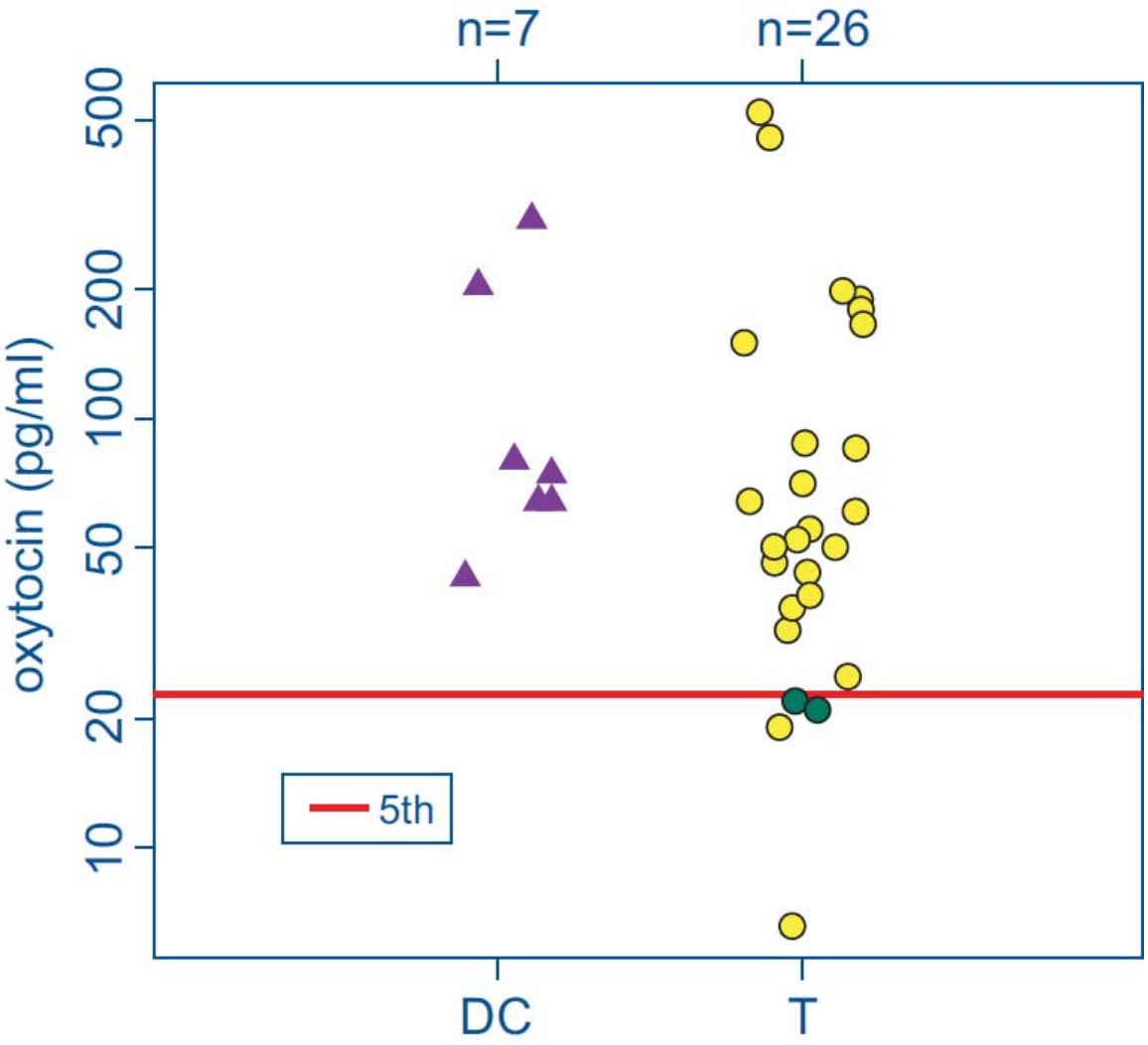

Figure 3. Oxytocin has been shown to play a role in multiple aspects of maternal, social, and romantic bonding and to have significant anxiolytic and anti-stress effects on social approach behavior and in socially challenging situations. It has also been linked to promotion of social recognition and interpretation of social signals. Extremely low concentrations of oxytocin have been linked to mental disorders characterized by severe social disturbances such as autism. None of the Veterans in the deployment control group, but four members of the mTBI group met our sub-5th-percentile criterion for oxytocin deficiency. The two subjects whose data are marked by green circles were those who were also found to have a functional vasopressin deficiency. The occurrence of deficiencies of both of these posterior pituitary hormones in the same individual suggest the possibility of disruption of the axons that carry these hormones through the pituitary stalk prior to release into the circulation.

Data Summary:

Subj.	LH	FSH	tTest	PRL	IGF-I	AVP	OT
	mIU/ml	U/L	ng/dl	ng/ml	ng/ml	pg/ml	pg/ml
T-2	2.03	---	669	9.6	185	12.3	181
T-4	2.03	2.06	252	54.9	110	8.0	88
T-8	2.72	4.02	401	11.9	141	0.2	44
T-10	1.97	2.43	520	12.3	230	0.2	22
T-12	7.27	5.70	715	13.0	198	12.0	55
T-13	1.92	1.18	253	6.3	187	6.4	50
T-14	2.66	2.51	390	12.0	151	0.5	19
T-16	2.64	4.01	380	21.5	126	0.9	190
T-21	4.00	4.48	588	12.8	227	0.0	21
T-23	2.24	4.34	463	7.2	146	2.1	25
T-26	2.11	2.64	264	15.3	86	8.4	0

Table 1. The table shows the hormone concentrations of the 11 of 26 Veterans with blast-induced mTBI who were found to have aberrant levels of one or more hormones. Five participants were found to have IGF-I concentrations consistent with GHD. Three of the mTBI group had luteinizing hormone and testosterone levels indicative of hypogonadism. Of these three, two had extremely low IGF-I levels, two had aberrant prolactin concentrations, and one had an oxytocin level below the sensitivity of the assay. In light of the fact that none of the deployment control subjects (although as yet, a small group) were found with abnormal levels of any of the hormones measured, we feel that our data strongly suggest that blast-induced mTBI carries a high risk for chronic pituitary dysfunction. (Please see Appendix 1 for more detail and interpretation.)

Problems in Accomplishing the Tasks

There has been one significant problem in performing the tasks described in the Statement of Work. That problem has been the lack of availability of a sufficient number of appropriate blood samples in the repository from which our samples are drawn. This study is dependent on the repository for samples, demographic information, and screening data. The problem stemmed from a temporary cessation of subject recruitment for the large mTBI imaging study that generates the samples in the repository. The delay was caused by the necessity for major revision of the IRB application for that study. Approval has now been obtained from both the VA Puget Sound Health Care System IRB and the University of Washington IRB. Recruitment for the imaging study has been successfully reinitiated, and additional samples are now available for use in this project. During Year Two we began generating data from these samples which are presented below. We are confident that sufficient samples will now be available to complete the study as proposed. We anticipate no additional problems.

Year Two Research Accomplishments

Pituitary and target organ hormones have now been measured in nine additional samples from Veterans with mTBI and eight additional samples from deployment control Veterans. We have analyzed the data for luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, IGF-I, prolactin, vasopressin, and oxytocin, and the analyses thus far confirm and extend the results we obtained during Year One. An abstract describing the new findings was accepted for presentation at the annual Experimental Biology meeting in Boston, April 20-24 of this year. The abstract was selected by the American Physiological Society for a press release to be issued in connection with the meeting. The abstract is listed among the Reportable Outcomes (p. 14) and included in Appendix 5.

In analyzing the Year Two results from the mTBI group we found that samples from two of the nine individuals met our criteria for hypogonadism. The criteria are a serum testosterone concentration below the 5th percentile of our community control reference range together with a serum LH concentration below the 10th percentile of the reference range. Two additional members of the mTBI group were found to meet our criteria for GHD, defined as a serum IGF-I concentration below the age-adjusted 10th percentile of the reference group value. Although data analyses have not been completed for all of the hormones, results so far show that 44.4% of this new subset of participants with mTBI have hormone concentrations consistent with either hypogonadism or GHD. Although 42% of the original subset of mTBI subjects were found with hormonal abnormalities, only 30.8% were found with abnormalities in this axis.

One of the eight members of the deployment control group was found to have serum hormone levels meeting the criteria for both hypogonadism and GHD. This is in contrast to the findings in our first subset of deployment control participants, none of seven of whom were found with any hormonal abnormalities.

The overall percentage of participants meeting criteria for GHD or hypogonadism in each of the two subject groups for all samples measured thus far are shown in Figure 4. The overall results confirm our initial conclusion that Veterans who sustain blast mTBI during deployment are at significantly greater risk for PTHP than deployed Veterans without blast exposure.

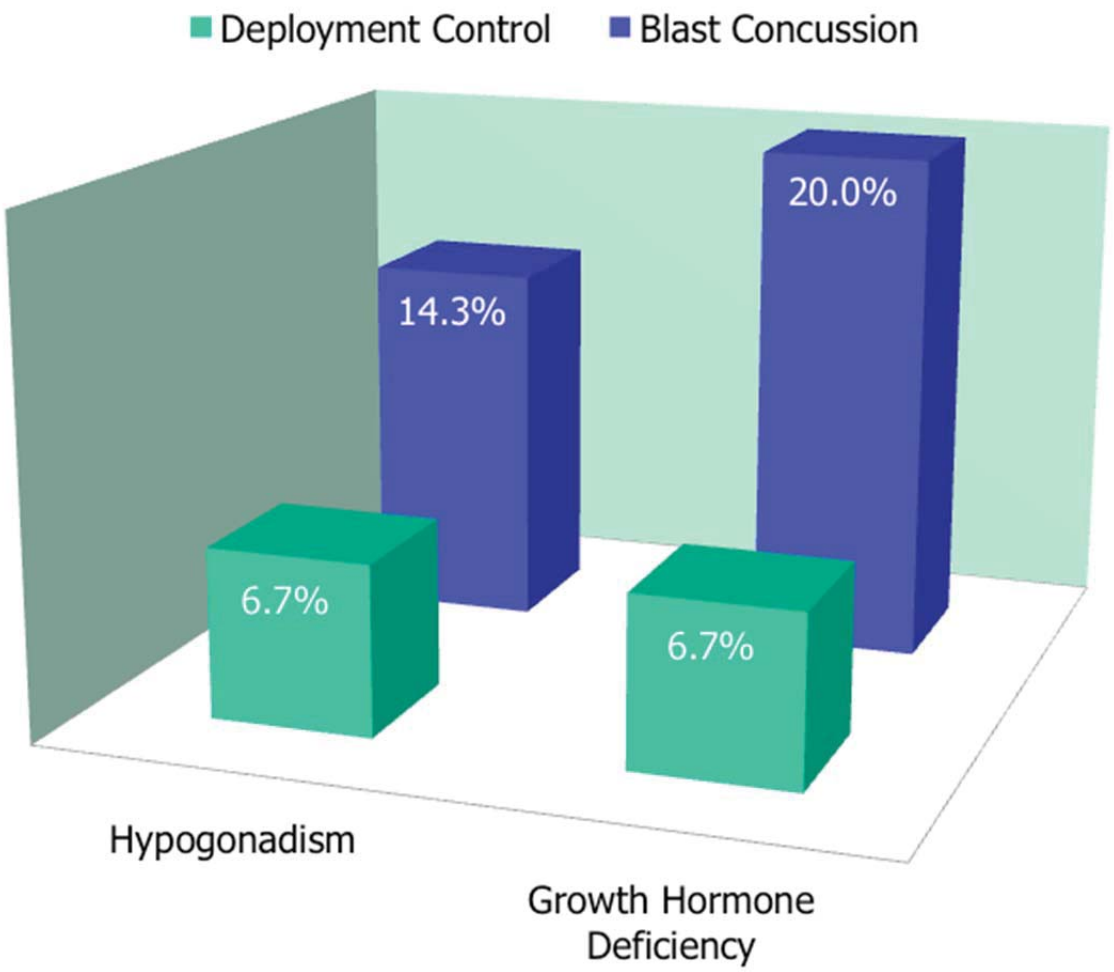

Figure 4. Results for all samples analyzed to date show that 14.3% (5/35) of mTBI subjects and 6.7% (1/15) of deployment control subjects met criteria for hypogonadism. Criteria for GHD were met by 20.0% (7/35) of mTBI subjects and 6.7% (1/15) of deployment control subjects.

Task 1: Completed. All regulatory approvals required for the study have been obtained.
Task 2: In Progress, some results available. Procurement of samples has been completed for 65 of the target sample of 100 community controls.
Task 3: In Progress, some results available. Hormone assays and identification of deficiencies have been completed for samples from 59 of 65 community control subjects that have been procured.
Task 4: In progress, some results available. Performance of assays and tabulation and analysis of data have been completed for 35 mTBI and 15 deployment control subjects.
Task 5: In progress, some results available. Individual hormone deficiencies have been identified for most subjects from whom samples have been procured, and are on-going for recently acquired samples.

Results based on the performance of Tasks 1-5 have been presented and published (See Reportable Outcomes, p. 13)

KEY RESEARCH ACCOMPLISHMENTS:

Year One:

- Determined that 11 of 26, or 42% of Veterans who had sustained blast mTBI during deployment to Iraq or Afghanistan had abnormal hormone levels consistent with hypopituitarism. None of seven Veterans of deployment to these regions without blast exposure were found to have any hormonal abnormalities.
- Concluded that blast mTBI carries a high risk for PTHP, some of the symptoms of which are the symptoms of which include fatigue, mood disturbances, anxiety and depression, irritability, insomnia, memory loss, social isolation, and decreased quality of life.
- Published these findings in the peer-reviewed journal *Frontiers in Neurology* (Appendix 1).
- Delivered seven presentations of these findings. Three of these presentations were made at international meetings, and in two cases the abstracts were published.
- Began consultation with personnel at the Defense Centers of Excellence for Psychological Health & Traumatic Brain Injury (DCoE) in the preparation of clinical guidelines for screening and diagnosis of neuroendocrine dysfunction resulting from blast mTBI.
- Received funding for a 4-year VA Rehabilitation Research & Development Merit Review Award based to a large extent on the perceived importance of the results of the work on this project.

Year Two:

- Delivered four presentations of this work including one at an international meeting that resulted in a published abstract.
- Performed additional data collection and analysis confirming our earlier findings of a high prevalence of hypogonadism and GHD after blast mTBI.
- Consultation on clinical guidelines for neuroendocrine dysfunction resulted in publication of a Clinical Practice Recommendation, a Pocket Guide for Primary Care Practitioners, and Provider Training Resources for neuroendocrine dysfunction posted on the DCoE website and distributed to Military Health Service providers. (See Reportable Outcomes and Appendices 6, 7 and 8.)
- Began collaboration with investigators at the Naval Military Health Center to continue and expand investigation of the prevalence of GHD and hypogonadism resulting from blast mTBI and to investigate potential associations of hormonal abnormalities with particular constellations of demographic, medical history, injury mechanism, and injury-specific data. (See Reportable Outcomes and Appendix 9.)
- Acceptance of abstract for presentation at the Experimental Biology annual meeting in Boston, April 20-24, and selection of the abstract by the American Physiological Society for a press release. The presentation is entitled “Prevalence of chronic hypopituitarism after blast concussion.” (Appendix 5)

REPORTABLE OUTCOMES:

Oral and Poster Presentation and Abstracts: Year One

1. "Chronic hypopituitarism after blast concussion mild traumatic brain injury in Iraq/Afghanistan combat Veterans." Charles W Wilkinson, Elaine R Peskind, Elizabeth A Colasurdo, and Jane B Shofer. Oral Presentation: 93rd Annual Meeting & Expo of The Endocrine Society, Boston Convention & Exhibition Center, Boston, MA, June 4-7, 2011.
Abstract published in *Endocrine Reviews* **32** (03_MeetingAbstracts): OR16-4, 2011 (Appendix 2)
http://edrv.endojournals.org/cgi/content/meeting_abstract/32/03_MeetingAbstracts/OR16-4?sid=611ee69b-229e-4ea6-8d33-6f794557b3b7

2. "Pituitary dysfunction after traumatic brain injury (TBI): relevance for psychological health and rehabilitation." Charles W. Wilkinson. Oral Presentation, Case Conference: Butler Hospital, Warren Alpert Medical School of Brown University, Providence, RI, June 10, 2011.

3. "Pituitary dysfunction in OIF/OEF Veterans with repetitive blast mild traumatic brain injury." Charles W. Wilkinson. Oral Presentation in Symposium: Structural and Functional Neuroimaging, Pituitary Dysfunction, and Animal Modeling in Blast Concussion Mild Traumatic Brain Injury. Elaine R. Peskind, Rajendra Morey, Charles W. Wilkinson, and David G. Cook. 3rd Federal Interagency Conference on Traumatic Brain Injury, Washington Hilton, Washington, DC, June 13-15, 2011.

4. "Blast concussion mTBI, hypopituitarism, and psychological health in OIF/OEF Veterans." Charles W. Wilkinson. Oral Presentation: Military Operational Medicine Research Program (MOMRP)/Joint Program Committee for Military Operational Medicine (JPC5) In Progress Review (IPR), Hilton Garden Inn, Frederick, MD, July 27, 2011.

5. "Pituitary dysfunction after blast concussion: relevance for psychological health and rehabilitation." Charles W. Wilkinson. Oral Presentation: National Intrepid Center of Excellence (NICoE) Grand Rounds, NICoE, National Naval Medical Center, Bethesda, MD, July 28, 2011.

6. "Chronic pituitary dysfunction after blast-related mild traumatic brain injury." Charles W. Wilkinson, Elaine R. Peskind, Elizabeth A. Colasurdo, Kathleen F. Pagulayan, and Jane B. Shofer. Poster Presentation: American College of Neuropsychopharmacology (ACNP) 50th Annual Meeting, Hilton Waikoloa Village, Waikoloa, HI, December 4-8, 2011.
Abstract published in *Neuropsychopharmacology* **36:**S407–S408, 2011 (Appendix 3)
http://www.nature.com/npp/journal/v36/n1s/full/npp2011293a.html

7. “Chronic pituitary dysfunction associated with cognitive and neuropsychiatric deficits after blast-related concussion.” Charles W. Wilkinson, Kathleen F. Pagulayan, Jane B. Shofer, and Elaine R. Peskind. Poster Presentation: 22nd Pacific Coast Brain Injury Conference, Sheraton Vancouver Wall Centre, Vancouver, BC, Canada, February 15-17, 2012.

Peer-reviewed Publication: Year One

“High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury.” Charles W. Wilkinson, Kathleen F. Pagulayan, Eric C. Petrie, Cynthia L. Mayer, Elizabeth A. Colasurdo, Jane B. Shofer, Kim L. Hart, David Hoff, Matthew A. Tarabochia, and Elaine R. Peskind. *Front Neurol* **3**:11, 2012. Published online 2012 February 7. Prepublished online 2011 December 27. doi: 10.3389/fneur.2012.00011 PMCID: PMC3273706 (Appendix 1) (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3273706/?tool=pubmed)

Oral and Poster Presentation and Abstracts: Year Two

1. “Prevalence and characteristics of chronic pituitary dysfunction after blast-related mild traumatic brain injury.” Charles W. Wilkinson, Elaine R. Peskind, Elizabeth A. Colasurdo, Kathleen F. Pagulayan, and Jane B. Shofer. Oral Presentation: Ninth World Congress on Brain Injury, Edinburgh International Conference Centre, Edinburgh, Scotland, March 21-25, 2012.
Abstract published in *Brain Injury* **26**:732 (Appendix 4)
http://informahealthcare.com/doi/pdf/10.3109/02699052.2012.660091

2. “Chronic pituitary hormone abnormalities after blast-induced mild traumatic brain injury in combat Veterans: a psychiatric concern?” Charles W. Wilkinson. Oral Presentation, Grand Rounds: University of Washington Department of Psychiatry and Behavioral Sciences, Harborview Medical Center, Seattle, WA, April 6, 2012.

3. “Hormonal abnormalities after blast concussion in Veterans: implications for quality of life.” Charles W. Wilkinson. Oral Presentation in Symposium: Overview of VA/UW Blast-related Traumatic Brain Injury Research Program. Lance Stewart, Elaine R. Peskind, Charles W. Wilkinson, and David G. Cook. VA Puget Sound Health Care System, Seattle, WA, April 9, 2012.

4. “Hormonal abnormalities after blast concussion in Veterans: implications for quality of life.” Charles W. Wilkinson. Oral Presentation, Research Seminar: Geriatric Research, Education and Clinical Center, VA Puget Sound Health Care System, Seattle, WA, April 9, 2012.

5. Accepted for presentation: “Prevalence of chronic hypopituitarism after blast concussion.” Charles W. Wilkinson, Elizabeth A. Colasurdo, Kathleen F. Pagulayan, Jane B. Shofer, Elaine R. Peskind. Poster

Presentation: Experimental Biology 2013, Boston Convention & Exhibition Center, Boston, MA, April 20-24, 2013. (Appendix 5)

Funding Applied for and Received Based on Work Supported by this Award

VA Rehabilitation Research & Development Merit Review Award.
Application Number: 1I01RX000509-01A1.
Principal Investigator: Charles W. Wilkinson, PhD
Project Title: Pituitary dysfunction, behavioral symptoms, and quality of life after blast mTBI.
Period: April 1, 2012- March 31, 2016.
Estimated Award Total: $932,347

Products of Coordination with Other Organizations Conducting Related Work: Year Two

Consultation with Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury:
In October, 2011, I was contacted by Therese West, a member of the Defense Centers of Excellence (DCoE) TBI Clinical Standards of Care Directorate. The Directorate was preparing a treatment algorithm and Clinical Practice Recommendation for primary care physicians in the MHS to educate and recommend screening for endocrine dysfunction following mild TBI and I was asked to consult on the project. Ms. West later requested that I review drafts of the Clinical Practice Recommendation, Pocket Guide for Primary Care Practitioners (PCP), and Provider Training Resources (PowerPoint training slide program). My review was completed and submitted to the DCoE. After multi-level review was completed, the three documents were posted on the DCoE website in May, 2012, and distributed to all providers in the Military Health Service. (Appendices 6, 7, and 8). Our publication in *Frontiers of Neurology* (Appendix 1) resulting from the current project is cited in the final Clinical Practice Recommendation and Provider Training Resources.

Collaboration with Investigators at the Naval Medical Research Center
Contact was initiated with three investigators from the Naval Medical Research Center (NMRC) in San Diego (LCDR Andrew MacGregor, PhD, MPH; Mary Clouser, MD, MPH; and Michael Galarneau, MS) to collaborate to obtain selected serum samples from the Department of Defense Serum Repository (DoDSR) maintained by the Armed Forces Health Surveillance Center (AFHSC). The DoDSR receives and stores serial serum specimens related to operational deployments worldwide which are made available to qualified DoD researchers upon acceptance of an application proposal. The AFHSC retains demographic, occupational, and medical information linked to the serum samples in the repository. The NMRC maintains the Expeditionary Medical Encounter Database (EMED), which contains clinical records completed by providers at forward-deployed medical facilities and including those of combatants with serious injuries who are subsequently evacuated to higher levels of care, as well as those with mild injury who are returned to duty. The clinical records provide details about the injury incident, such as injury mechanism, as well as the number, type, and severity of injuries, including TBI. The proposed

collaboration with NMRC investigators will involve the selection of Marines who experienced mTBI in Iraq or Afghanistan as well as deployed non-blast-exposed Marines selected on the basis of the EMED records. Matching serum samples will be requested from the DoDSR.

The hypothesis of the proposed study is that serum hormone deficiencies characteristic of hypogonadism and growth hormone deficiency (GHD) are significantly more frequent in US Marines who have sustained blast-related mild traumatic brain injury (mTBI), i.e., concussion, while deployed in Iraq, Operation Iraqi Freedom (OIF) or Afghanistan, Operation Enduring Freedom (OEF) (mTBI group) than in similarly deployed Marines not exposed to blast trauma (Non Blast Exposed (NBE) group). This hypothesis will be tested by measuring luteinizing hormone (LH), testosterone, and insulin-like growth factor-I (IGF-I) in my laboratory in predeployment and postdeployment serum samples from Marines in each of the two groups. The study will also investigate potential associations of hormonal abnormalities after blast mTBI with particular constellations of demographic, medical history, injury mechanism, and injury-specific data to determine to what extent each of these factors or combinations of factors best predict the occurrence of chronic pituitary dysfunction after blast concussion.

The NMRC investigators and I have submitted an application and proposal to AFHSC for serum samples and demographic data with which to perform this project. The text of the proposal is attached (Appendix 9). A decision on the acceptance of the proposal is expected by the end of April, 2013.

CONCLUSION:

In this preliminary study, 42% of participants with blast mTBI showed evidence of PTHP as determined by basal hormone measurements. The prevalence of hypopituitarism from all causes in the general population has been estimated at 300 cases per million, or 0.03%. PTHP is associated with symptoms easily mistaken for those of PTSD including fatigue, mood disturbances, anxiety and depression, irritability, insomnia, memory loss, social isolation, and decreased quality of life. Muscular weakness, erectile dysfunction, infertility, deleterious effects on body composition, and diminished cardiovascular function are also frequent consequences. These symptoms, if they result from PTSD, are often resistant to successful treatment. However, if some or all of the symptoms are indeed of neuroendocrine origin and are appropriately diagnosed as consequences of PTHP, they can be treated successfully with hormone replacement. Therefore, failure to consider the diagnosis of PTHP may result in inappropriate and ineffective treatment of the symptoms.

In light of the fact that PTHP is associated with a constellation of symptoms and diminished quality of life similar to PTSD, these findings support the value of routine screening for pituitary dysfunction after blast concussion. Neuroendocrine screening shows promise for:

a. identifying those individuals whose symptoms are of neuroendocrine origin,

b. directing diagnostic and therapeutic strategies that might otherwise remain unconsidered,

c. and markedly facilitating recovery and rehabilitation after blast-induced, and other forms, of traumatic brain injury.

The "so what" is that – IF the symptoms of a number approximating our preliminary figure of 42% of warriors who sustain a blast concussion are due to neuroendocrine dysfunction – hundreds of thousands may be spared a lifetime of serious psychological and physiological disability if routine hormonal screening after blast mTBI becomes standard procedure. Such a practice also holds the possibility of redirecting millions of dollars from potentially ineffective treatments toward other interventions that may improve the psychological and physical health of many more warriors and Veterans.

REFERENCES:

All relevant references are included in the Reference section of the manuscript in Appendix 1 (p. 19), which begins on p. 27.

APPENDICES:

Appendix 1: *Frontiers in Neurology* article, "High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury." (Page 19)

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High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury

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Studies of traumatic brain injury from all causes have found evidence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones at least 1 year after injury, in 25–50% of cases. Most studies found the occurrence of posttraumatic hypopituitarism (PTHP) to be unrelated to injury severity. Growth hormone deficiency (GHD) and hypogonadism were reported most frequently. Hypopituitarism, and in particular adult GHD, is associated with symptoms that resemble those of PTSD, including fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, cognitive deficiencies, and decreased quality of life. However, the prevalence of PTHP after blast-related mild TBI (mTBI), an extremely common injury in modern military operations, has not been characterized. We measured concentrations of 12 pituitary and target-organ hormones in two groups of male US Veterans of combat in Iraq or Afghanistan. One group consisted of participants with blast-related mTBI whose last blast exposure was at least 1 year prior to the study. The other consisted of Veterans with similar military deployment histories but without blast exposure. Eleven of 26, or 42% of participants with blast concussions were found to have abnormal hormone levels in one or more pituitary axes, a prevalence similar to that found in other forms of TBI. Five members of the mTBI group were found with markedly low age-adjusted insulin-like growth factor-I (IGF-I) levels indicative of probable GHD, and three had testosterone and gonadotropin concentrations consistent with hypogonadism. If symptoms characteristic of both PTHP and PTSD can be linked to pituitary dysfunction, they may be amenable to treatment with hormone replacement. Routine screening for chronic hypopituitarism after blast concussion shows promise for appropriately directing diagnostic and therapeutic decisions that otherwise may remain unconsidered and for markedly facilitating recovery and rehabilitation.

Keywords: traumatic brain injury, hypopituitarism, blast, concussion, growth hormone, pituitary

INTRODUCTION

Recent studies investigating chronic pituitary dysfunction resulting from TBI have reported a prevalence of posttraumatic hypopituitarism (PTHP) ranging from 5 to 95% with a median of 35%, the variation being primarily due to differences in screening criteria (Bavisetty et al., 2008; Srinivasan et al., 2009; Berg et al., 2010; Englander et al., 2010; High et al., 2010; Kokshoorn et al., 2010, 2011; Krahulik et al., 2010; Park et al., 2010; Pavlovic et al., 2010; Reimunde et al., 2011; Schneider et al., 2011). Pituitary hormone disorders are frequently among the immediate consequences of TBI; some resolve during the following months while a smaller proportion of new dysfunctions emerge (Agha et al., 2005; Aimaretti et al., 2005; Schneider et al., 2006, 2011; Tanriverdi et al., 2006, 2008b; Klose et al., 2007; Krahulik et al., 2010). By ∼6 months subsequent to TBI, the pattern of pituitary deficits is considered to be relatively permanent.

The risk factors and the mechanisms, other than immediate trauma-induced tissue damage and subsequent edema, for chronic hypothalamo-pituitary dysfunction due to TBI are unclear. Roles for polymorphisms in apolipoprotein E genotype (*APOE*), inflammatory processes – both systemic and neural, and anti-hypothalamic (AHAs) and anti-pituitary antibodies (APAs) have been proposed, and each has empirical support.

There is evidence that the apolipoprotein E (*APOE*) ε3/ε3 genotype may be associated with a reduced risk of TBI-related hypopituitarism. *APOE* ε3 is the most common of the three alleles and is found in more than half of the general population. The ε2 and ε4 alleles have been associated with altered risks for Alzheimer's disease, hyperlipoproteinemia, and atherosclerosis. Pituitary dysfunction in patients with TBI has been found to be significantly less prevalent in individuals with the *APOE* ε3/ε3 genotype (17.7%)

than in patients with other genotypes (41.9%; $p = 0.01$; Tanriverdi et al., 2008a).

Evidence for the involvement of APAs and/or AHAs in the development of chronic PTHP comes from two studies. APAs were detected in 44.8% of patients who had completed a 3-year-follow-up after TBI and in none of the healthy control subjects, and the prevalence of hypopituitarism was significantly higher in APA-positive (46.2%) than APA-negative TBI patients (12.5%; $p = 0.04$; Tanriverdi et al., 2008b). In another study of active and retired boxers, AHAs were detected in 21.3% and APAs in 22.9% of boxers, whereas no evidence of APAs or AHAs was found in control subjects (Tanriverdi et al., 2010a).

It is well established that TBI results in the acute induction of both neural and systemic inflammatory responses and consequent anti-inflammatory counter-responses (Lu et al., 2009; Ziebell and Morganti-Kossmann, 2010). In addition, animal studies provide evidence of the development of a chronic inflammatory state after TBI. Three months after moderate focal brain injury in rats, persistent major histocompatibility complex (MHC)-II up-regulation, mononuclear phagocytosis, and elevated interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) synthesis were observed in large areas of the ipsilateral hemisphere (Holmin and Mathiesen, 1999). In another study, 2 months after cortical contusion injury to the medial frontal cortex of rats, IL-1β was significantly increased in the cortex and hypothalamus compared with a sham–trauma group, and glial fibrillary acidic protein (GFAP) was elevated in the cortex, hypothalamus, and anterior pituitary of the TBI group (Kasturi and Stein, 2009).

In general, the frequency of occurrence of pituitary hormone abnormalities has not been found to be related to the severity of the trauma (Lieberman et al., 2001; Agha et al., 2004a; Aimaretti et al., 2004, 2005; Bondanelli et al., 2004; Schneider et al., 2006; Park et al., 2010; Kokshoorn et al., 2011), although there have been reports of a positive relationship (Kelly et al., 2000; Klose et al., 2007). Of the traumatic brain injuries sustained by ∼1.7 million Americans annually (Faul et al., 2010), 75% are considered mild TBI (mTBI; National Center for Injury Prevention and Control, 2003).

Mild TBI is defined by the American Congress of Rehabilitation Medicine (ACRM) as a head trauma resulting in any one of the following: loss of consciousness (LOC) for 30 min or less, alteration of mental state for up to 24 h (being dazed, confused, disoriented, etc.), or loss of memory for events immediately before or after the trauma (American Congress of Rehabilitation Medicine, 1993). The terms mTBI and concussion are frequently used interchangeably (National Center for Injury Prevention and Control, 2003; Department of Veterans Affairs/Department of Defense, 2009).

Mild TBI-related chronic pituitary dysfunction has been reported in boxers and kick boxers subjected to repetitive head injuries. In a preliminary study, 45% of professional boxers were found with apparent growth hormone deficiency (GHD), but no other pituitary hormone deficiencies were observed (Kelestimur et al., 2004). In a larger study of active and retired boxers 18% had pituitary hormone deficiencies in one or more axes (Tanriverdi et al., 2008c). An investigation of pituitary dysfunction in amateur kick boxers revealed GH and/or adrenocorticotropin (ACTH) deficiencies in 27.3% of the athletes (Tanriverdi et al., 2007).

In 2010, the injuries in 80% of over 30,000 U.S. military service members medically diagnosed with TBI were classified as mTBI (Military Health System, 2011), and mTBI sustained from explosive blasts is one of the most common combat injuries resulting from deployment to Iraq or Afghanistan. About 10–20% of returnees report having experienced at least one blast concussion (Tanielian et al., 2008; Terrio et al., 2009).

The extensive documentation of the high prevalence of hypopituitarism after TBI from all causes and the absence of any published studies of the frequency of PTHP after blast-related mTBI provided the rationale for this investigation of hypopituitarism in U.S. Veterans of combat in Iraq and/or Afghanistan who have experienced at least one blast concussion.

MATERIALS AND METHODS

PARTICIPANTS AND SAMPLE ACQUISITION

The VA Puget Sound Health Care System (VAPSHCS) Institutional Review Board and the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO) approved the subject protocol with a waiver of informed consent. All plasma and serum samples, demographic, and blast exposure data were obtained from an established biorepository entitled "Alzheimer's Disease Research Center (ADRC) Participant Registry and Sample Repository." All subjects whose samples were utilized had consented to have their samples and data used in future research of this type.

The mTBI Veteran participants (T group) whose samples were obtained from the repository were a convenience sample of 26 male Veterans recruited from VAPSHCS, all of whom had documented hazardous duty experience in Iraq and/or Afghanistan with the U.S. Armed Forces and had reported experiencing at least one blast exposure in the war zone that resulted in acute mTBI as defined by ACRM criteria (American Congress of Rehabilitation Medicine, 1993) except that Glasgow Coma Scale scores were not obtained in the combat setting. Samples from the repository were also collected from seven male Veterans who had been deployed to Iraq and/or Afghanistan but who had not been exposed to blast and had no history of TBI. These individuals made up the deployment control (DC) group.

Additional samples from the repository which were used to establish normal hormonal reference ranges had been collected from 59 cognitively normal male community volunteers recruited from the ADRC, all of whom were medically healthy and had Mini-Mental State Examination scores of 29.4 ± 1.0 (mean ± SEM; range 27–30); Clinical Dementia Rating scores of zero; no evidence or history of cognitive or functional decline; and no history of blast exposure or head injury. These samples were used only for the establishment of normative hormone concentrations with our assay methods. Resting blood samples had been collected from all participants between 9:00 and 10:00 a.m., at least 30 min after the insertion of an intravenous catheter in an antecubital vein.

None of the Veteran or community control participants had a history of blast exposure, head injury with LOC greater than 30 min; penetrating head wound; seizure disorder; insulin-dependent diabetes; current or past DSM-IV diagnoses of schizophrenia, other psychotic disorders, bipolar disorder, or dementia; or a DSM-IV diagnosis of alcohol or other substance abuse or dependence within the previous 3 months. Participants using medications likely to affect brain function, such as opioids,

benzodiazepines, or anti-depressants, were asked not to take those medications for 24 h prior to blood sampling.

BLAST EXPOSURE ASSESSMENT

Blast exposure and mTBI histories had been obtained from mTBI Veteran participants during a clinical interview in which specific inquiries were made regarding total number of blast exposures accompanied by acute symptoms of TBI and/or LOC in Iraq and/or Afghanistan and lifetime history of non-blast exposure head injuries accompanied by acute symptoms of TBI and/or LOC (e.g., sports or motor vehicle accident-related concussion).

NEUROLOGICAL ASSESSMENT

All subjects underwent a full neurological examination, including the Unified Parkinson's Disease Rating Scale (UPDRS) motor section (Martínez-Martín et al., 1994). Olfactory function was assessed using the Brief Smell Identification Test (B-SIT; Doty et al., 1996).

HORMONE MEASUREMENT

Blood samples for the measurement of plasma hormone concentrations were collected between 9:00 and 10:00 a.m. in chilled tubes containing ethylenediaminetetraacetic acid (EDTA), placed on ice, and centrifuged at 4°C prior to removal of the plasma fraction. Blood samples for measurement of serum hormones were collected in serum-separator tubes, allowed to clot at room temperature for 10 min, and centrifuged to isolate serum. Serum and plasma samples were aliquoted and stored at −70°C. Twelve pituitary or target-organ hormones were measured in these samples. The type, source, and performance characteristics of the assay kits used for the measurement of hormone concentrations in serum and plasma are shown in **Table 1**. ACTH, cortisol, thyroid-stimulating hormone (TSH), oxytocin, and vasopressin concentrations were determined in plasma; free thyroxine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, insulin-like growth factor-I (IGF-I), growth hormone, and prolactin were measured in serum.

CLINICAL LAB DATA

Measurements of plasma and urine osmolality were not available but urine specific gravity was measured and used as a criterion to determine functional vasopressin insufficiency.

STATISTICAL ANALYSIS AND CRITERIA FOR PITUITARY DEFICIENCIES

The criteria for PTHP, derived using hormone measurements from the 59 community control participants are shown in **Table 2**. For each hormone, age-adjusted percentiles based on the lognormal distribution from community control participants were estimated and dysfunction in each of seven hormonal axes was defined (R Development Core Team, 2011). Hypopituitarism was defined as a dysfunction in at least one of these seven axes. These criteria were

Table 1 | Sources and characteristics of hormone assay kits.

Assay	Kit name	Manufacturer	Location
ACTH	ACTH Immunoradiometric (IRMA) Assay	Scantibodies Laboratory	Santee, CA, USA
Cortisol	GammaCoat™Cortisol ^{125}I RIA	Diasorin	Stillwater, MN, USA
FSH	DELPHIA hFSH	Perkin Elmer	Waltham, MA, USA
GH	hGH-ELISA, Ultra-Sensitive	DSL	Webster, TX, USA
IGF-I	IGF-I RIA	IBL America	Minneapolis, MN, USA
LH	ImmuChem™Coated Tube LH ^{125}I RIA	MP Biomedicals	Costa Mesa, CA, USA
Oxytocin	Oxytocin EIA Kit – Extraction-free	Peninsula Labs/Bachem	San Carlos, CA, USA
Prolactin	ImmuChem™Coated Tube Prolactin ^{125}I IRMA	MP Biomedicals	Costa Mesa, CA, USA
Testosterone	Total Testosterone	Siemens Diagnostics	Los Angeles, CA, USA
Thyroxine	Free Thyroxine (FT_4) Microplate EIA	MP Biomedicals	Costa Mesa, CA, USA
TSH	ImmuChem™Coated Tube TSH ^{125}I IRMA	MP Biomedicals	Costa Mesa, CA, USA
Vasopressin	Vasopressin Direct RIA	ALPCO	Salem, NH, USA

Hormones	Assay type	Sample type	Assay size	Sample size	Assay range	Sensitivity	Intra-assay CV	Inter-assay CV
ACTH	IRMA	Plasma	100 Tubes	200 µl	9–1693 pg/ml	<1.0 pg/ml	4.05	6.66
Cortisol	RIA	Plasma	100 Tubes	10 µl	1–60 µg/dl	0.21 µg/dl	7.03	9.20
FSH	Fluoroimmunoassay	Serum	96 Wells	25 µl	0.98–256 U/l	0.05 U/l	2.33	1.87
GH	EIA	Serum	96 Wells	100 µl	4.5–500 pg/ml	0.66 pg/ml	6.00	5.40
IGF-1	RIA	Serum	100 Tubes	100 µl	0.16–10.0 ng/ml	0.02 ng/ml	2.97	10.30
LH	RIA	Serum	100 Tubes	100 µl	2.5–200 mIU/ml	1.5 mIU/ml	5.90	7.90
Oxytocin	EIA	Plasma	96 Wells	50 µl	0–630 pg/ml	6.5 pg/ml	9.36	13.67
Prolactin	IRMA	Serum	100 Tubes	25 µl	2.5–100 ng/ml	2.5 ng/ml	5.13	8.08
Testosterone	Solid-phase RIA	Serum	100 Tubes	50 µl	20–1600 ng/dl	4 ng/dl	3.40	7.90
Thyroxine	EIA	Serum	96 Wells	50 µl	0.45–7.6 ng/dl	0.05 ng/dl	6.83	6.47
TSH	IRMA	Plasma	100 Tubes	200 µl	0.2–50 µIU/ml	0.04 µIU/ml	4.10	5.23
Vasopressin	RIA	Plasma	100 Tubes	400 µl	1.25–80 pg/ml	0.1 pg/ml	6.00	9.90

Table 2 | Screening criteria for identifying abnormal circulating hormone levels.

Axis	Criteria using lognormal distribution of community control reference sample
Adrenal insufficiency	Cortisol < 10th percentile (6.7 μg/dl), and ACTH < 10th percentile (18 pg/ml)
Thyroid deficiency	Free T-4 < 5th percentile (0.87 ng/dl), and TSH < 50th percentile (2.39 μIU/ml)
Hypogonadism	Total testosterone < 5th percentile (330 ng/dl) and either LH or FSH < 10th percentile (2.3 mIU/ml, 1.3 U/l, respectively) OR (total testosterone < 5th percentile and prolactin > 95th percentile (32 ng/ml)
Vasopressin abnormality	Vasopressin > 95th percentile (9.46 pg/ml) OR vasopressin < 5th percentile (0.27 pg/ml) and urine specific gravity < 1.003
Prolactin abnormality	Prolactin > 95th percentile (32.0 ng/ml) OR prolactin < 5th percentile (6.7 ng/ml)
GH deficiency	IGF-1 < age-adjusted 10th percentile (SDS < −1.4)
Oxytocin deficiency	Oxytocin < 5th percentile (22.7 pg/ml)
Hypopituitarism	Abnormalities in at least one of these 7 axes

modeled after those used in published studies of hypopituitarism after TBI from all causes.

RESULTS

PLASMA/SERUM HORMONE SCREENING EVALUATIONS

Eleven of 26 mTBI subjects (T), or 42%, were found to have abnormal hormone values in at least one axis. As reported in earlier studies of PTHP, deficiencies in the growth hormone-IGF-I and pituitary–gonadal axes were observed most frequently (Bavisetty et al., 2008; Dusick et al., 2008; Schneider et al., 2008; Englander et al., 2010; Kokshoorn et al., 2010; Krahulik et al., 2010; Park et al., 2010; Pavlovic et al., 2010; van der Eerden et al., 2010).

Markedly low IGF-I levels are strong indicators of adult GHD (Juul et al., 1997; Hartman et al., 2002; Hadjadj et al., 2007; Ho, 2007; Prodam et al., 2008; Tanriverdi et al., 2011; Zgaljardic et al., 2011). The red line in **Figure 1** represents the cutoff level used to define our criterion for subnormal IGF-I levels indicative of probable GHD. The cutoff level was defined to be an IGF-I concentration below the age-adjusted 10th percentile level [equivalent to an SD score (SDS) below −1.4] of the community control reference sample (**Figure 1**; **Table 2**). Five Veteran participants with mTBI (T-4, T-8, T-16, T-25, and T-28) were found to have serum IGF-I concentrations below this cutoff line. None of the Veteran participants in the DC group were found to have subnormal age-adjusted IGF-I levels (**Figure 1**).

Three participants with mTBI (T-4, T-13, and T-28) were found with abnormal hormonal profiles indicating probable hypogonadism. The criteria were a total testosterone concentration less than the 5th percentile of the reference sample together with an LH or FSH level below the 10th percentile reference level (**Figure 2**; **Table 2**). T-4 and T-28 also had the lowest two IGF-I levels among the participants (T-4: 126 ng/ml, SDS = −2.325; T-28: 86 ng/ml, SDS = −2.989). Elevated prolactin levels in conjunction with low testosterone are also indicative of hypogonadism. A serum prolactin concentration markedly higher than the 95th percentile of the reference sample was found in serum from participant T-4. A subnormal prolactin concentration (<5th percentile), also associated with sexual dysfunction, was measured in serum from T-13.

None of the Veterans in the DC group were found to have hormone levels indicative of hypogonadism. One participant in the DC group was found with a total testosterone concentration below the 5th percentile reference standard and another had an LH concentration below the 10th LH percentile, but neither exhibited the combined gonadotropin and testosterone deficiencies consistent with hypogonadism.

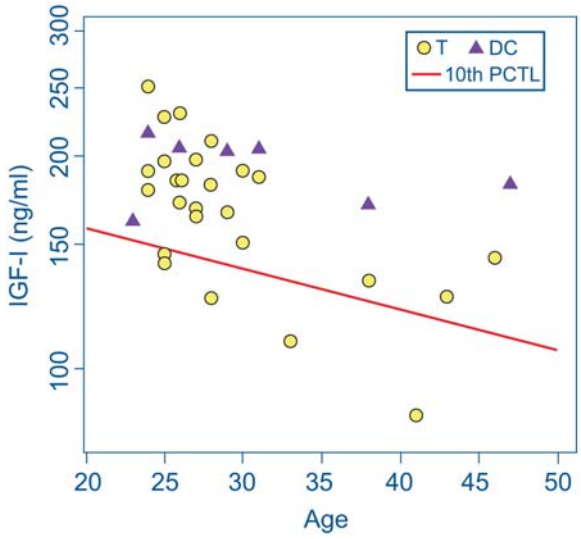

FIGURE 1 | IGF-I concentrations in serum from deployment control (DC) participants (triangles) and participants with mTBI (T, circles). The screening criterion for growth hormone deficiency was an IGF-I level below the age-adjusted 10th percentile of IGF-I concentration (diagonal red line) in the community control reference group. Serum IGF-I values of five Veterans with mTBI fell below this cutoff line. None of the DC group met this criterion.

None of the Veteran participants in either the T or DC group exhibited abnormalities in the hypothalamic-pituitary–adrenocortical or hypothalamic-pituitary–thyroid axis (**Table 3**). The corticotrophs and thyrotrophs are located in the protected median wedge of the anterior pituitary and are anatomically less vulnerable to injury than gonadotropin- and GH-secreting cells. This differential anatomical vulnerability correlates well with the frequency of chronic hormonal abnormalities observed after TBI (Bavisetty et al., 2008; Blair, 2010; Krahulik et al., 2010).

In addition to the findings of anterior pituitary hormone abnormalities in six Veteran participants with mTBI, eight instances of anomalous posterior pituitary hormone levels were

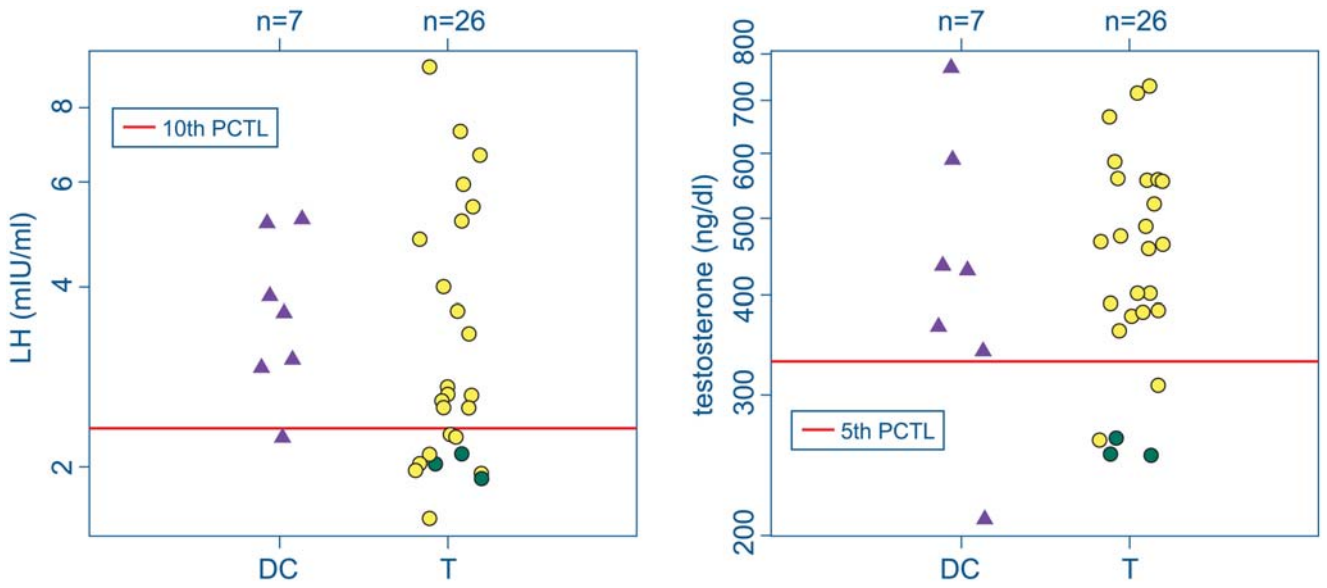

FIGURE 2 | Serum LH (left) and testosterone (right) in the deployment control (DC, triangles) and mTBI (T, circles) groups. Screening criteria for hypogonadism: LH (or FSH) levels below the 10th percentile of the control range together with testosterone below the 5th percentile (red lines). Green circles mark data from 3 T subjects falling below both cutoffs. No DC subjects met both criteria.

found in six Veterans in the mTBI group, one of whom, T-28, also had evidence of presumptive GHD and hypogonadism. The plasma oxytocin concentration was unmeasurably low in this individual (**Table 3**). None of the Veterans in the DC group were found to have abnormal posterior pituitary hormone values.

Three additional participants from the mTBI group (T-10, T-14, and T-22) also were found to have circulating oxytocin concentrations below the reference sample's 5th percentile level. Two of these participants, T-10 and T-22, also met our criteria for arginine vasopressin (AVP) deficiency: plasma vasopressin concentration below the 5th percentile of the reference level in combination with urine specific gravity less than 1.003. In addition, plasma vasopressin concentrations in participants T-2 and T-12 were abnormally elevated above the 95th percentile of the reference group.

DEMOGRAPHICS, DEPLOYMENT HISTORY, BLAST EXPOSURE, AND MEDICATION USE

After completion of hormone measurement and identification of Veterans with apparent hypopituitarism, participants in the T group were divided into two subgroups, based on the presence or absence of hormone abnormalities, for comparison of demographic, deployment history, blast exposure, and medication use data with each other and with the DC group. The three groups of Veteran participants did not differ in age, education, or body mass index at the time of enrollment, and the two mTBI subgroups did not differ significantly from one another on any of the measures of deployment history or blast exposure (**Table 4**).

CONCURRENT MEDICATIONS

Medications with potential neuroendocrine effects taken by mTBI subjects found to have indications of hypopituitarism were opiates (2/11), prazosin (2/11), selective serotonin reuptake inhibitors (SSRIs; 4/11), serotonin and norepinephrine reuptake inhibitors (SNRIs; 2/11), hypnotics (2/11), atypical antipsychotics (1/11), calcium channel blockers for migraine (1/11), benzodiazepines (1/11), and mirtazapine (1/11). Five subjects in this group were not taking any neuroactive medications. Medications with potential neuroendocrine effects taken by mTBI subjects found to have hormone levels within normal ranges were opiates (1/15), prazosin (4/15), SSRIs (3/15), SNRIs (2/15), mirtazapine (1/15), trazodone (1/15), benzodiazepines (1/15), and disulfiram (1/15). Nine subjects in this group were not taking any neuroactive medications. Medications with potential neuroendocrine effects taken by DC subjects were opiates (1/7), SSRIs (1/7), and SNRIs (1/7). Five subjects in this group were not taking any neuroactive medications.

DISCUSSION

Our findings in this preliminary study support the hypothesis that blast mTBI carries a risk of PTHP similar to that found in several previous studies of hypopituitarism in the general population after TBI from all causes. We have found that blood samples from 11 of 26, or 42% of Veterans of combat in Iraq or Afghanistan had abnormal circulating hormone concentrations consistent with PTHP. Five participants with blast mTBI exhibited evidence of anterior pituitary dysfunction, five additional subjects had anomalous posterior pituitary hormone levels, and the eleventh was found to have both anterior and posterior pituitary hormonal abnormalities. In contrast, none of the seven Veterans of deployment to Iraq and/or Afghanistan in the study who did not experience blast trauma – the DC group – were found to have evidence of pituitary dysfunction.

As Kokshoorn et al. (2010) pointed out in their review of 14 investigations of PTHP conducted between 2000 and 2009, these early studies used a broad variety of screening criteria that were sometimes described in general terms rather than with specifically

Table 3 | Plasma or serum hormone concentration for each participant.

Subject	Age	#BE	ACTH (pg/ml)	Cort (μg/dl)	LH (mIU/ml)	FSH (U/l)	tTest (ng/dl)	PRL (ng/ml)	TSH (μIU/ml)	fT-4 (ng/dl)	IGF-I (ng/ml)	GH (pg/ml)	AVP (pg/ml)	OT (pg/ml)
T-1	24	11	24	6.6	2.58	0.46	473	12.5	1.70	1.29	190	58	3.4	64
T-2	26	6	20	11.9	2.03	–	669	9.6	1.92	1.67	185	71	12.3	181
T-3	27	10	22	10.2	5.15	2.05	557	13.0	1.59	1.59	164	50	4.0	166
T-4	33	15	19	7.5	2.03	2.06	252	54.9	1.17	1.22	110	11	8.0	88
T-5	38	102	24	12.8	2.11	2.33	362	14.9	1.16	1.18	133	0	0.4	71
T-6	46	5	29	12.1	1.95	1.41	402	11.1	1.08	1.09	143	152	0.7	61
T-7	26	20	28	14.1	3.34	1.63	559	12.0	2.26	1.29	172	223	0.0	39
T-8	25	21	35	11.3	2.72	4.02	401	11.9	1.13	1.55	141	294	0.2	44
T-9	24	102	39	12.0	4.81	3.28	730	14.4	1.16	1.05	251	1288	8.0	52
T-10	26	20	30	9.6	1.97	2.43	520	12.3	2.41	1.39	230	68	0.2	22
T-11	28	9	31	10.2	1.64	2.38	382	9.2	1.30	1.22	182	0	1.1	36
T-12	27	15	27	9.9	7.27	5.70	715	13.0	1.57	1.38	198	60	12.0	55
T-13	31	7	40	7.8	1.92	1.18	253	6.3	2.24	1.14	187	0	6.4	50
T-14	30	6	36	8.8	2.66	2.51	390	12.0	3.75	1.13	151	310	0.5	19
T-15	27	11	16	7.4	2.27	3.56	377	10.1	1.40	1.14	168	42	4.4	85
T-16	28	66	25	11.7	2.64	4.01	380	21.5	0.65	1.52	126	0	0.9	190
T-17	25	18	26	11.2	9.32	3.00	465	17.1	1.26	1.25	197	0	4.8	151
T-18	24	7	30	14.2	3.65	2.21	556	12.2	1.27	1.30	179	60	4.3	32
T-19	30	1	32	18.6	5.44	3.01	457	11.7	1.55	1.13	190	66	0.0	46
T-20	28	3	17	25.0	6.65	3.91	309	10.4	0.79	1.31	210	1696	7.9	519
T-22	25	4	21	17.6	4.00	4.48	588	12.8	1.09	1.24	227	110	0.0	21
T-23	29	52	11	8.7	2.52	2.55	554	8.9	1.34	1.35	166	95	4.0	199
T-25	25	12	8	7.7	2.24	4.34	463	7.2	1.42	1.23	146	813	2.1	25
T-26	26	11	9	6.8	5.94	1.14	488	8.4	0.81	1.18	185	42	0.9	457
T-27	43	5	29	7.5	2.52	3.89	263	7.1	0.60	1.04	126	13	2.6	50
T-28	41	12	15	11.1	2.11	2.64	264	15.3	1.22	1.11	86	375	8.4	0

*Shaded values indicate hormone axis abnormalities as defined in **Table 2**. #BE, number of self-reported blast exposures meeting ACRM criteria for mTBI during military career; ACTH, adrenocorticotropin; Cort, cortisol; LH, luteinizing hormone; FSH, follicle-stimulating hormone; tTest, total testosterone; PRL, prolactin; TSH, thyroid-stimulating hormone; fT-4, free thyroxine; IGF-I, insulin-like growth factor-I; GH, growth hormone; AVP, vasopressin; OT, oxytocin.*

defined cutoffs. We attempted to use relatively conservative and explicitly defined criteria based on the distribution of specific hormone concentrations measured in a reference population. We did not employ provocative testing but used criteria based on measurement of both pituitary hormones and their target-organ hormones when possible, e.g., a combination of measurements of total testosterone, LH, FSH, and prolactin to screen for hypogonadism.

It should be cautioned that the determinations of basal hormone concentrations, such as those made in this study, are meant to be screening tools, and are not intended to be, nor should they be interpreted to be, diagnostic in the absence of clinical assessment. Measurement of basal circulating hormone concentrations is generally considered an appropriate screening tool for provisional identification of deficient thyroid function, hypogonadism, and prolactin and oxytocin deficiencies. Diagnosis of significant abnormalities of vasopressin secretion normally require confirmation by measures of plasma and/or urine osmolality, urine specific gravity (UGS), and/or the administration of a water deprivation test. Although provocative testing is generally considered necessary for diagnosis of sAI and GHD, measurement of basal cortisol and IGF-I concentrations remain valuable screening tools to identify individuals most likely to benefit from additional testing and clinical referral. Evaluation of clinical signs and symptoms are essential for definitive diagnoses in all cases.

Previous studies have found GHD to be the most prevalent chronic endocrine consequence of TBI, and it carries with it a potentially large range of symptoms. Provocative testing is considered to be a requisite for the reliable diagnosis of GHD because serum GH concentrations measured in the morning are not valid indicators of daily secretion or somatotroph function. GH secretion occurs predominantly during sleep, and morning levels are generally very low but punctuated unpredictably by short secretory bursts (Van Cauter et al., 1992). However, GH stimulates hepatic production of IGF-I that provides a useful index of somatotroph function. IGF-I concentrations have low diagnostic sensitivity for identifying GHD but are highly specific. The presence of normal IGF-I values cannot be used to exclude GDH because it is often diagnosed in individuals with normal or even elevated IGF-I levels. However, markedly low age-adjusted levels of IGF-I are strongly indicative of GHD (Juul et al., 1997; Hadjadj et al., 2007; Ho, 2007; Prodam et al., 2008; Tanriverdi et al., 2011; Zgaljardic et al., 2011). Circulating IGF-I concentrations decline markedly with increasing age, and this decline must be taken into account when interpreting them.

Table 4 | Mean ± SEM and (range) for demographic, deployment, and blast exposure data for each group of participants.

	DC ($n = 7$)	mTBI without PTHP($n = 15$)	mTBI with PTHP($n = 11$)
A. DEMOGRAPHICS			
Age (years)	31.1 ± 3.3 (23–47)	29.7 ± 1.8 (24–46)	28.8 ± 1.5 (25–41)
Education (years)	14.0 ± 0.7 (12–17)	13.3 ± 0.4 (11–16)	13.6 ± 0.5 (12–16)
Marital status	3/7 Married, 4/7 single	7/15 Married, 4/15 single, 2/15 divorced, 2/15 unknown	7/11 Married, 1/11 single, 1/11 separated, 2/11 unknown
Body mass index (BMI)	28.5 ± 2.1 ($n = 5$)[†]	27.9 ± 1.3 ($n = 14$)[†]	29.0 ± 1.3 ($n = 10$)[†]
B. DEPLOYMENT HISTORY			
Number of deployments	1.7 ± 0.4 (1–3)	1.9 ± 0.2 (1–4)	2.1 ± 0.3 (1–3)
Time between first and second deployments (months)	14.3 ± 7.0 (3.5–27.5) ($n = 3$)	15.9 ± 3.1 (4.0–39.5) ($n = 10$)	15.4 ± 2.4 (7.5–30.0) ($n = 8$)
Time between second and third deployments (months)	6.0 ± 1.0 (5.0–7.0) ($n = 2$)	8.0 ± 2.0 (6–12) ($n = 3$)	7.6 ± 2.0 (3.0–12.5) ($n = 4$)
Time between third and forth deployments (months)		8.0 ± 0.0 ($n = 1$)	
Total deployment time (months)	13.0 ± 1.8 (7–21)	18.7 ± 2.2 (7–37)	18.2 ± 1.7 (11–27)
C. BLAST EXPOSURE			
Deployment blast exposures meeting ACRM criteria for mTBI	0	11.1 ± 3.3 (1–52)	14.6 ± 5.4 (4–66)
Blast exposures meeting ACRM criteria during military career	0.3 ± 0.3 (0–2)	24.5 ± 8.7 (1–102)	16.7 ± 5.2 (4–66)
Blast exposures with LOC	0	1.3 ± 0.3 (0–4)	0.6 ± 0.2 (0–2)
Lifetime events with LOC	0.1 ± 0.1 (0–1)	3.1 ± 0.7 (0–11)	1.3 ± 0.4 (0–3)
Time since last blast exposure (months)		45.2 ± 4.2 (14–66)	47.4 ± 4.3 (20–67)

The Veterans with blast mTBI (T group) were divided into two subgroups based upon the presence or absence of abnormal hormonal profiles suggesting PTHP.[†] *BMIs were not obtained for all participants.*

Studies using receiver operating characteristic (ROC) analysis to compare the diagnostic accuracy of IGF-I relative to diagnosis of GHD based on provocative testing of GH secretion have reported a diagnostic specificity of 100% with IGF-I SDS cutoffs of −1.3 (Corneli et al., 2007) or −1.7 (Maghnie et al., 2005).

The individuals classified here as having a high probability of GHD all had values less than −1.4 SDs below the age-adjusted means of the reference sample. The high specificity of IGF-I measurements at this level assures a very low likelihood of false positives in diagnosing GHD. However, in light of the low sensitivity of IGF-I concentrations in predicting GHD, it is probable that some Veteran participants with normal IGF-I levels may be growth hormone deficient.

The long-term sequelae of GHD in adults for health, quality of life (QoL), and morbidity are multifaceted and complex. Low GH secretion has been associated with behavioral symptoms and deficits in several cognitive domains (Popovic et al., 2004; Falleti et al., 2006; Pavlovic et al., 2010). GHD also has significant deleterious effects on body composition and cardiovascular function. Adult GHD is associated with lipidemia, reduced lean body mass, and increased adiposity. Even partial GHD in adult patients is associated with adverse lipid profiles and early atherosclerosis (Colao et al., 2006a,b; Colao, 2008). Impairment in QoL is also a prominent feature of adult GHD, especially in the areas of energy and vitality (McGauley, 1989; Kelly et al., 2006; Bushnik et al., 2007; Svensson et al., 2007; Bavisetty et al., 2008). Adult GHD is also associated with reductions in muscle volume and strength, decreased physical mobility, fatigue, sleep impairment, social isolation, depression, lowered metabolic rate, low sexual drive, and reduced aerobic capacity (Rosén et al., 1994; Mossberg et al., 2008).

Many of the symptoms of GHD can be successfully ameliorated or reversed by growth hormone replacement therapy. Five retrospective studies have shown that the risk of premature death from cardiovascular disease is elevated in patients with GHD (Svensson et al., 2004a). The increased risk factors such as adverse lipid profiles, increased blood pressure, abnormal body composition, increased body weight, increased coagulability, and increased markers of inflammation have all been shown to improve with GH replacement (Svensson et al., 2004a, 2007; Götherström et al., 2007a; Verhelst and Abs, 2009). GH replacement has been found to be effective in reversing cognitive impairments in several domains including simple motor speed, information processing speed, episodic memory, mental flexibility, verbal memory, and executive functioning in patients after TBI (High et al., 2010; Reimunde et al., 2011). GH replacement also normalizes muscle strength and increases bone mineral density (Götherström et al., 2007b, 2009), improves psychiatric functioning by ameliorating depression, intensity of interpersonal sensitivity, hostility, paranoid ideation, and anxiety (Maric et al., 2010), and improves QoL (Svensson et al., 2004b, 2007; Kreitschmann-Andermahr et al., 2008).

Three of the Veteran participants in the T group met our criteria for hypogonadism: a total testosterone concentration less than the 5th percentile of the reference sample together with an LH or FSH level below the 10th percentile reference level. In our very small sample, the occurrence of hypogonadism was found to be next highest in frequency to that of GHD, as was the case in several of the studies of PTHP after TBI from all causes in the general population (Bavisetty et al., 2008; Dusick et al., 2008; Krahulik et al., 2010; Park et al., 2010; Tanriverdi et al., 2010b).

Hypogonadism has significant deleterious consequences in addition to its adverse effects on fertility, psychosexual function, and general well being. Testosterone deficiency in males is associated with decreased energy and motivation, muscle weakness, reduced lean body mass, and impaired exercise tolerance (Agha and Thompson, 2005). In addition, a recent large epidemiological study has shown that untreated hypogonadism is associated with premature mortality secondary to cardiovascular disease (Tomlinson et al., 2001).

One mTBI participant, T-4, was found to have a highly elevated concentration of prolactin, 2.5 times higher than the next highest concentration measured in the T group and more than four times higher than the highest value in the DC group. Hyperprolactinemia has been causally linked with hypogonadism, specifically by reducing LH and FSH secretion, blocking LH stimulation of testicular testosterone secretion, and producing oligospermia by reducing FSH levels, resulting in hypoactive sexual desire and erectile dysfunction.

Prolactin is the only anterior pituitary hormone that is under predominantly inhibitory control. Its secretion is suppressed by dopamine, and in the absence of this inhibition, prolactin is released at high levels. Hyperprolactinemia frequently results from the use of antipsychotic medications that act as antagonists at dopamine D2 receptors (Holt, 2008; Inder and Castle, 2011).

Participant T-4 had been taking quetiapine, an atypical antipsychotic with fast dissociation kinetics at the D2 receptor [released from D2 within 12–24 h (Seeman, 2010)] that results only in low and transient prolactin secretion (Carboni et al., 2011). It has not generally been associated with hyperprolactinemia in clinical use (Haddad and Wieck, 2004; Byerly et al., 2007; Bushe et al., 2010) although a prevalence of 22% was found in one study (Montgomery et al., 2004). It is often referred to as a dopamine-sparing antipsychotic, and although it is much less potent in elevating prolactin levels than several other antipsychotics (e.g., haloperidol and risperidone), it may have prolactin-elevating effects in some individuals, perhaps including participant T-4.

One of the Veterans with mTBI was found to have a subnormal (less than 5th percentile) prolactin concentration. Hypoprolactinemia is rare in the general population, but it too has been associated with sexual dysfunction, primarily arteriogenic erectile dysfunction and premature ejaculation (Corona et al., 2009).

We found no evidence of dysfunction in the thyroid or adrenal axes as a result of blast mTBI. Previous studies of pituitary deficiencies after TBI from all causes have generally reported a lower prevalence of TSH and adrenocorticotropin (ACTH) deficiencies than of GH or gonadotropin deficits (Bavisetty et al., 2008; Blair, 2010; Krahulik et al., 2010). This pattern may be due in part to the location of pituitary corticotrophs and thyrotrophs in the gland's protected median wedge and their blood supply via both the long hypophysial portal vessels and the inferior hypophysial artery. GH-secreting somatotrophs, on the other hand, are anatomically more vulnerable to damage because of their location in the pituitary's exposed lateral wings and their primary dependence on vascular input from the portal system alone. Gonadotrophs are distributed throughout the anterior pituitary, and the cells in the lateral wings are relatively vulnerable.

In addition to the six participants with hormonal levels consistent with hypogonadism and/or GHD, six of the Veterans with mTBI (including one with anterior pituitary hormonal abnormalities) exhibited abnormal plasma vasopressin and/or oxytocin concentrations. Oxytocin concentrations below the 5th percentile value of the community control group were observed in four of the mTBI participants. Two of the four also exhibited indications of vasopressin deficiency as defined by vasopressin levels below the 5th percentile of the community reference group together with urine specific gravity less than 1.003. The occurrence of deficits of both vasopressin and oxytocin in two participants suggests the possibility of disruption of the pituitary stalk or hypothalamic damage in these individuals. In addition, elevated plasma vasopressin concentrations above the reference 95th percentile were measured in two subjects.

In several studies, elevated cerebrospinal fluid (CSF) or peripheral vasopressin concentrations have been associated with PTSD, depression, schizophrenia, and other psychiatric disorders, but a causal relationship has not been established (Purba et al., 1996; van Londen et al., 1997; Coccaro et al., 1998; Merali et al., 2006; de Kloet et al., 2008; Goekoop et al., 2009; Heinrichs et al., 2009). In contrast, there is evidence from both animal and human studies for the positive association of oxytocin levels with social bonding, attenuation of stress responses in socially relevant challenges, mediation of social support, and positive social interactions (Heinrichs et al., 2009; Campbell, 2010).

Our finding of a high frequency of abnormal peripheral hormone levels after blast mTBI in this preliminary study is consistent with the investigations cited above, in which the prevalence of pituitary dysfunction fell in the 30–60% range in 11 of 22 reports. However, in general, those studies focused exclusively on anterior pituitary dysfunction. Although few studies have investigated the prevalence of chronic posterior pituitary hormonal abnormalities after TBI, most (Agha et al., 2004b, 2005; Krahulik et al., 2010), but not all (Bondanelli et al., 2004), found significant evidence of damage in that lobe as well. In this study we found significant anterior pituitary dysfunction in 23.1% of Veterans with mTBI and abnormal posterior pituitary hormone levels in 23.1% of this group as well. In contrast, the prevalence of hypopituitarism in the general adult population ranges between 290 and 455 cases per million (Regal et al., 2001).

The only other ongoing study of hypopituitarism after blast mTBI of which we are aware recently reported preliminary results based on two retrospective chart reviews. Of 147 Marines with blast-related mTBI screened approximately 1 year or more after injury, 25% were found to have abnormal levels of one or more anterior pituitary hormones (Stokes and Gallagher, 2011).

The Veteran groups in this study are highly similar in demographic characteristics and share the common experience of

deployment under highly stressful and dangerous conditions accentuated by extreme heat and the burden of heavy equipment even when not actively engaged in combat. Despite these commonalities, the experience of blast trauma and the combat situations in which these exposures occur have major long-term consequences well beyond those of deployment to Iraq or Afghanistan. The considerable overlap between the constellations of symptoms typical of chronic hypopituitarism and persistent post-concussive symptoms (PPCS), in addition to the similarities of both to PTSD, make accurate diagnosis of the etiology, progression, and identifiable differences between the conditions of critical importance for successful treatment, recovery, and rehabilitation (Masel, 2005).

The consequences of undiagnosed and untreated pituitary hormone deficiencies are manifold and significant and include diminished QoL, cognitive deficiencies, fatigue, sleep disturbance, sexual dysfunction, deleterious changes in metabolism and body composition, behavioral and psychiatric problems including anxiety, irritability, social isolation, depression, and increased cardiovascular mortality. PTHP, unlike PTSD and PPCS, is readily treatable if correctly diagnosed, and many of its symptoms can be reversed or ameliorated with appropriate hormone replacement therapy.

Several of the authors of previous studies of hypopituitarism after TBI have advocated routine endocrine evaluation after brain injury (Masel, 2004; Leal-Cerro et al., 2005; Schneider et al., 2005; Urban et al., 2005; Powner et al., 2006; Behan and Agha, 2007; Ho, 2007; Behan et al., 2008; Tanriverdi et al., 2008b, 2010b; Blair, 2010; Krahulik et al., 2010; Park et al., 2010). A recent review of the literature (Guerrero and Alfonso, 2010) stated that because "many of the symptoms of hypopituitarism are similar to those of TBI, it is important to make clinicians caring for combat veterans aware of its occurrence. . . All patients who had a TBI of any severity, should undergo baseline hormonal evaluation."

To our knowledge, this is the first published study of basal hormonal evaluation of combat Veterans with blast mTBI, and our preliminary findings of PTHP in 42% of study participants supports the advisability of routine screening for hypopituitarism after brain injury in both military and civilian populations. Routine provocative testing for sAI and for GHD, the most frequently observed chronic endocrine disorder resulting from TBI, is neither economically nor practically viable. However, measurement of basal concentrations of a panel of pituitary and target-organ hormones similar to those performed here may provide valuable preliminary indications of those individuals most likely to benefit from further clinical evaluation. Similar preliminary screening for pituitary dysfunction after blast concussion shows promise for appropriately directing diagnostic and therapeutic decisions that otherwise may remain unconsidered and for markedly facilitating recovery and rehabilitation.

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Chronic Hypopituitarism after Blast Concussion Mild Traumatic Brain Injury in Iraq/Afghanistan Combat Veterans

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Studies of civilian traumatic brain injury (TBI) from all causes have found evidence of chronic hypopituitarism, as defined by deficient production of one or more pituitary hormones measured at least one year after injury, in 33-50% of cases (1). Its occurrence has not been found to be related to trauma severity (1,2). Hypopituitarism is associated with non-specific behavioral symptoms that can be mistaken for PTSD, including fatigue, anxiety, depression, irritability, insomnia, poor concentration and memory, and decreased quality of life (1). Despite these findings, the prevalence of hypopituitarism after blast concussion mild TBI, the signature injury of combat in Iraq and Afghanistan, has not yet been investigated. Mild TBI (mTBI) is characterized by brief loss of consciousness or loss of memory for events surrounding the trauma or any alteration of mental state (disorientation, confusion). In order to determine the frequency of pituitary dysfunction after blast concussion mTBI, we are measuring pituitary and target organ hormones in blood samples from Iraq/Afghanistan Veterans with mTBI taken at least one year subsequent to their last blast exposure. Most have experienced multiple blast exposures. Criteria for identifying abnormal circulating levels of LH, FSH, total testosterone, prolactin, ACTH, cortisol, TSH, free thyroxine, GH, IGF-I, and arginine vasopressin (AVP) were derived from RIA or EIA measurement of basal morning concentrations in a large group of male non-Veteran control subjects. In general, values below the 5th percentile or above the 95th percentile were defined as abnormal. When both pituitary and target organ hormones were measured for a given axis, a specific combination of criteria signaled dysfunction of that axis. Using the criteria defined in controls, 10 of 26 Veterans with blast mTBI were found to have abnormal hormone levels in one or more pituitary axes. Seven mTBI subjects exhibited deviant plasma AVP concentrations, either above or below the 5th-95th percentile normal range. The frequency of abnormally low or abnormally elevated AVP levels has been found to be relatively high in the acute stage of non-blast TBI, but it tends to decline with time. These preliminary findings suggest that the prevalence of hypopituitarism after blast concussion mTBI is similar to that in other forms of TBI, and that recovery and rehabilitation of blast-exposed Veterans may be facilitated by comprehensive screening for pituitary dysfunction.

(1) Ghigo E et al., Brain Inj, 2005; 19:711(2) Lieberman SA et al., J Clin Endocrinol Metab 2001; 86:2752

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152. Chronic Pituitary Dysfunction after Blast-related Mild Traumatic Brain Injury

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Background: Studies of civilian traumatic brain injury (TBI) from all causes have found evidence of chronic hypopituitarism, as defined by deficient production of one or more pituitary hormones measured at least one year after injury, in 25-50% of cases. Its frequency of occurrence has not been found to be related to trauma severity. The most common anterior pituitary dysfunctions reported were growth hormone deficiency (GHD) and hypogonadism. Hypopituitarism, and in particular adult GHD, is associated with non-specific behavioral symptoms that can be mistaken for PTSD, including fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, poor concentration and memory, and decreased quality of life. Despite the high frequency of hypopituitarism after civilian TBI, the prevalence of hypopituitarism after blast-related mild TBI, the signature injury of combat in Iraq and Afghanistan, has not yet been investigated. Mild TBI (mTBI) is characterized by brief loss or alteration of consciousness. The mechanisms of injury of blast mTBI are very complex and poorly understood. Blast is propagated directly through the skull and indirectly via blood vessels, and reflections of blast waves in a closed space can redirect and magnify their effects. The pituitary is vulnerable to compression due to its confinement in the sella turcica, and the narrow pituitary stalk (2-3 mm diameter) is subject to torsional and rotational forces resulting from brain movement.

Methods: In order to determine the frequency of pituitary dysfunction after blast-related mTBI, we are measuring pituitary and target organ hormones in blood samples taken from Iraq/Afghanistan Veterans with mTBI at least one year subsequent to their last blast exposure, and from Veterans after deployment in Iraq/Afghanistan without blast exposure. Criteria for identifying abnormal circulating levels of luteinizing hormone (LH), follicle-stimulating hormone, total testosterone, prolactin, adrenocorticotropin, cortisol, thyroid-stimulating hormone, free thyroxine, growth hormone, insulin-like growth factor-I (IGF-I), oxytocin, and arginine vasopressin (AVP) were derived from determinations of normative ranges of basal morning hormone concentrations in a group of male non-Veteran control subjects. In general, hormone concentrations below the 5th percentile or above the 95th percentile were defined as abnormal. When both pituitary and target organ hormones were measured for a given axis, a specific combination of criteria defined dysfunction of that axis.

Results: Based on the normative ranges defined by hormone measurements in control subjects, 11 of 26, or 42%, of Veterans with blast mTBI were found to have abnormal hormone levels in one or more

pituitary axes. Five Veterans with mTBI were found to have probable GHD, based on age-adjusted IGF-I concentrations below the 10th percentile concentration of the reference control group. Three Veterans in the mTBI group were found to have probable hypogonadism on the basis of abnormally low testosterone and LH concentrations. Six of the mTBI group were found to have abnormal levels of the posterior pituitary hormones oxytocin and/ or AVP. None of the non-blast-exposed Veterans were found to have hormone abnormalities.

Discussion: These preliminary findings suggest that the prevalence of hypopituitarism after blast-related mTBI is similar to that in other forms of TBI. Consistent with earlier studies of TBI from all causes, GH and gonadotropin deficiencies were most frequent. Posttraumatic hypopituitarism is associated with a constellation of neuropsychiatric symptoms and diminished quality of life similar to PTSD that are largely amenable to successful treatment with hormone replacement. Routine screening for pituitary dysfunction after blast mTBI shows promise for appropriately directing diagnostic and therapeutic decisions that may otherwise remain unconsidered and for markedly facilitating recovery and rehabilitation.

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Prevalence and Characteristics of Chronic Pituitary Dysfunction after Blast-related Mild Traumatic Brain Injury

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Objectives: Studies of civilian traumatic brain injury (TBI) from all causes have found evidence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones measured at least one year after injury, in 25–50% of cases. The most common pituitary disorders found were growth hormone deficiency (GHD) and hypogonadism. Hypopituitarism, and in particular adult GHD, is associated with non-specific behavioral symptoms that can be mistaken for PTSD, including fatigue, anxiety, depression, irritability, insomnia, sexual dysfunction, poor concentration and memory, and decreased quality of life. Despite the high frequency of pituitary dysfunction after civilian TBI, the occurrence of posttraumatic hypopituitarism after blast-related mild TBI (mTBI), an extremely common injury in modern military operations, has not been characterized. The objective of this study is to evaluate the prevalence and specific nature of pituitary hormone abnormalities consequent to blast mTBI.

Methods: Concentrations of twelve pituitary and target-organ hormones were measured by radioimmunoassay or enzyme-linked immunosorbent assay of blood samples taken from two groups of US military Veterans of combat in Iraq and/or Afghanistan. One group consisted of participants with blast-related mTBI whose last blast exposure was at least one year prior to entry in the study. The other group consisted of participants with similar military deployment experience but without blast exposure. Criteria for identifying abnormal circulating levels of luteinizing hormone (LH), follicle-stimulating hormone, total testosterone, prolactin, adrenocorticotropin (ACTH), cortisol, thyroid-stimulating hormone, free thyroxine, growth hormone, insulin-like growth factor-I (IGF-I), oxytocin, and arginine vasopressin (AVP) were derived from determinations of normative ranges in a group of male non-Veteran control subjects.

Results: Eleven of 26, or 42%, of participants with blast mTBI were found to have abnormal hormone levels relative to the normative ranges in one or more pituitary axes. Five members of the mTBI group were found to have probable GHD, based on their age-adjusted IGF-I concentrations. Three of the mTBI subjects were found to have abnormally low testosterone and LH concentrations consistent with hypogonadism. Six of the mTBI group were found to have abnormal levels of the posterior pituitary hormones oxytocin and/ or AVP. None of the non-blast-exposed Veterans had any abnormal hormone concentrations.

Conclusions: These preliminary findings suggest that the prevalence of hypopituitarism after blast-related mTBI is similar to that in other forms of TBI. Pituitary hormone deficiencies are associated with a constellation of neuropsychiatric symptoms and diminished quality of life similar to those of PTSD but which are amenable to successful treatment with hormone replacement. Routine screening for pituitary dysfunction after blast mTBI shows promise for appropriately directing diagnostic and therapeutic decisions that may otherwise remain unconsidered and for markedly facilitating recovery and rehabilitation.

Supported by DoD PT0753; GRECC, Northwest Network MIRECC, and R&D Service, VA Puget Sound HCS.

Abstract accepted for presentation at Experimental Biology 2013, April 20-24, Boston, MA

Prevalence of chronic hypopituitarism after blast concussion

Charles W. Wilkinson[1,3], Elizabeth A. Colasurdo[1], Kathleen F. Pagulayan[2,3], Jane B. Shofer[3], Elaine R. Peskind[2,3]. [1]Geriatric Research, Education and Clinical Center, [2]VA Northwest Network Mental Illness Research, Education and Clinical Center, VA Puget Sound Health Care System, Seattle, WA, [3]Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA

Studies of traumatic brain injury (TBI) from all causes have reported a prevalence of chronic hypopituitarism, defined by deficient production of one or more pituitary hormones measured at least one year after injury, of 25-50%. Hypopituitarism is associated with fatigue, anxiety, depression, insomnia, cognitive dysfunction, and deleterious changes in body composition and cardiovascular function. However, the prevalence of hypopituitarism after blast concussion/mild TBI (mTBI) has not previously been investigated. We measured twelve pituitary and target organ hormones in blood samples from Veterans of deployment to Iraq or Afghanistan with mTBI and from Veterans of deployment without blast exposure. Criteria for identifying abnormal hormone levels were derived from measurement of basal hormone concentrations in male non-Veteran control subjects. Preliminary results indicate that 42% of individuals with blast mTBI exhibited abnormal hormone levels suggestive of pituitary dysfunction, with the most prevalent deficiencies being consistent with hypogonadism and growth hormone deficiency. These findings of a high frequency of hypopituitarism after blast concussion similar to that found in other forms of TBI provide support for the value of routine hormonal screening in facilitating the recovery and rehabilitation of blast-exposed Veterans. Supported by DoD PT0753 and the Dept. of Veterans Affairs.

DCoE Clinical Recommendation
March 2012

Indications and Conditions for Neuroendocrine Dysfunction Screening Post Mild Traumatic Brain Injury

Introduction & Background

More than 233,345 traumatic brain injuries (TBI) have occurred in the military from 2000 through December 2011.[1] The majority of these (80-85 percent), have been classified as mild TBI (mTBI). Most patients with mTBI recover completely within three months or less of injury. However a small subset of these individuals experience persistent symptoms and difficulty in rehabilitation, particularly in the setting of co-occurring disorders.[2,3] Neuroendocrine dysfunction (NED) may be a contributing factor in the setting of prolonged symptoms or difficult rehabilitation following mTBI.[4,5]

NED following TBI is the result of direct trauma or biochemical response that interferes with the normal production and regulation of inter-related hormonal processes. The anterior pituitary is the most vulnerable and most often affected endocrine structure.[3,4,5] The neuroendocrine pathways most frequently affected in mTBI are growth hormone and gonadotropin.[3,4,6,7,8] Deficiency of these hormones in adults may lead to symptoms such as fatigue, weight gain, low blood pressure, low libido, loss of muscle mass and amenorrhea. The screening strategy described below is recommended to identify most individuals with NED related to mTBI.[4,5,6] The onset of NED can occur anytime between the event and up to 36 months post injury. NED may adversely affect prognosis and impede recovery from TBI.[6,8,9,10] The diagnosis of NED may be difficult and is sometimes not considered because the symptoms may significantly overlap with post-concussion syndrome as well as other co-occurring conditions such as sleep disorders, PTSD or depression.[6,11] Service members diagnosed with concussion who are experiencing persistent symptoms suggestive of NED for greater than three months (or new onset up to 36 months) following mTBI may benefit from post-injury NED screening.[6,8,11,12]

This Clinical Recommendation is intended to offer the health care provider an approach to identifying patients with mTBI who may benefit from further endocrine evaluation and care and is specifically intended to support the primary care provider. The recommendation is based on a review of current published literature as well as the proceedings of a December 2010 expert panel convened by DCoE that included clinical subject matter experts representing the military services, the Department of Veterans Affairs, DCoE and civilian sectors. It was reviewed and approved by the Defense Department's TBI Quad Services Cell, which includes TBI representation from the Air Force, Army, Marines and Navy.

Clinical Recommendation

- Consider NED in the differential diagnosis after confirmed mTBI when symptoms suggestive of NED persist for greater than three months (or new onset up to 36 months) following injury. These symptoms may include fatigue, insomnia, impaired cognition and memory loss, difficulty concentrating, emotional and mood disturbance.
- Symptoms of NED are similar to the symptoms of other post mTBI medical diagnoses such as sleep disorder, memory difficulties, depression, PTSD and /or post concussive syndrome.[12] Considering NED may avoid a delay in diagnosis and improve prognosis.[4,5,11]
- Anterior pituitary deficiencies account for the majority of chronic neuroendocrine disorders following mTBI. Growth hormone and gonadotropin deficiencies are most common, but TSH deficiency (secondary hypothyroidism) and ACTH deficiency (adrenal insufficiency) may occur as well (less than 10 percent of cases with TBI associated NED).[13] Therefore, the following screening strategy is recommended as a rational approach to the initial evaluation in the primary care environment.
- The following describes the typical symptoms suggestive of the previously stated neuroendocrine deficiencies.
  - » **Growth Hormone Deficiencies:** Characterized by loss of lean muscle mass and strength,

increased body fat around the waist, weight gain, reduced heart rate, low blood pressure, constipation, poor memory, lack of concentration, depression, anxiety, fatigue and decreased sex drive.

- » **Gonadotropin Deficiencies (LH/FSH/Testosterone/Estradiol):** Characterized by loss of libido, infertility, anemia, hair loss, decreased muscle mass and strength, amenorrhea and mood disorders.
- » **Adrenocorticotropic hormone deficiency:** Characterized by hypotension, weight loss, malaise and fatigue.
- » **TSH Deficiency:** Characterized by weight gain, cold intolerance, impaired short-term memory, dry skin and constipation.

- Recommended NED serum screening labs include*:
  - » 0800 Cortisol levels (<12 mcg/dl, recommend follow up)
  - » TSH — Thyroid Stimulating Hormone
  - » LH — Luteinizing Hormone
  - » FSH — Follicle Stimulating Hormone
  - » IGF — 1 Insulin–like Growth Factor
  - » FT4 — Free Thyroxine
  - » Testosterone (males only)
  - » Estradiol (females only)

** Local and lab specific reference ranges should be utilized to determine deficiencies*

- Post-injury screening for NED should only be used as one component of a thorough clinical evaluation by a qualified provider. It should not be used in isolation for clinical decision making.
- Referral to Endocrinology is advised if lab results suggest NED or if strong clinical suspicion of NED remains despite negative screening tests and other potential causes for symptoms have been excluded.

Conclusion

NED should be a considered following a confirmed diagnosis of TBI when a service member remains symptomatic beyond 3 months and/or becomes symptomatic up to 36 months after injury. NED screening studies should not be routinely ordered as a screening or diagnostic tool during the early post injury period. Screening for NED can provide valuable clinical insight leading to prompt treatment and improved overall prognosis for this subset of patients.

As with all clinical decisions, field and operational circumstances may at times require deviation from these recommendations.

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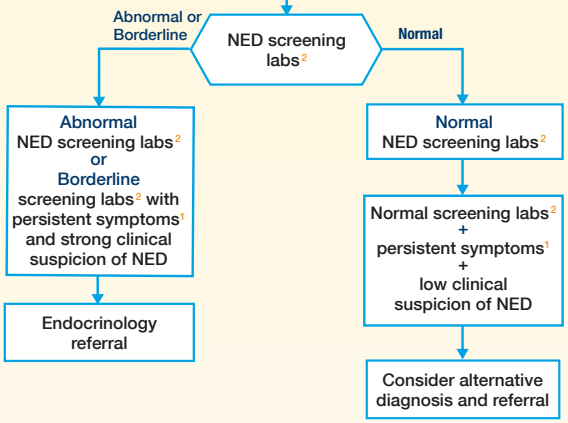
Neuroendocrine Dysfunction Screening Post Mild TBI

Neuroendocrine testing should be considered if there is a history of mild TBI (in accordance with the VA/DoD 2009 Evidence Based Clinical Practice Guideline: Management of Concussion/mild Traumatic Brain Injury) and the patient is experiencing continuing symptoms that are suggestive of NED[1] for greater than three months duration; or there is a new onset of symptoms suggestive of NED[1] up to 36 months following mild TBI.



[1] Symptoms that are suggestive of NED:

- Depression
- Emotional lability
- Anxiety
- Fatigue
- Poor memory
- Lack of concentration
- Loss of libido
- Infertility
- Amenorrhea
- Loss of muscle mass
- Increased body fat around the waist
- Weight gain/weight loss
- Low blood pressure
- Reduced heart rate
- Hair loss
- Anemia
- Constipation
- Cold intolerance
- Dry skin

[2] Recommended NED screening labs (local and lab specific reference ranges should be utilized to determine deficiencies):

- 0800 cortisol levels (<12 mcg/dl recommend follow up)
- LH (luteinizing hormone)
- FSH (follicle stimulating hormone)
- PRL (prolactin)
- IGF-1 (insulin-like growth factor)
- TSH (thyroid stimulating hormone)
- FT4 (free thyroxine)
- 0800 testosterone for males or estradiol for females

Neuroendocrine Dysfunction Screening Post Mild TBI

This fact sheet summarizes the clinical recommendation that was developed from the proceedings of the 2010 DCoE sponsored Neuroendocrine Sequelae and TBI Literature Review and Consensus Meeting. The complete clinical recommendation document and list of references can be accessed at: http://www.dcoe.health.mil/ForHealthPros/Resources.aspx

- Of the approximate 15% of individuals who experience a mild TBI and remain symptomatic, an estimated 15-30% develop NED
- While NED is more often associated with severe TBI, it is important to recognize that NED occurs with mild and moderate TBI as well
- The onset of NED symptoms may occur up to 36 months after injury
- Although multiple endocrine deficiencies have been reported, the most frequently identified in mild TBI are addressed in the DCoE clinical recommendation
- NED symptoms may overlap other medical and psychiatric diagnoses such as post concussive syndrome (headaches, dizziness, fatigue, irritability, anxiety, insomnia, loss of concentration, memory, noise and light sensitivity), sleep disorders, depression or post traumatic stress disorder (PTSD)
- Referral to an endocrinologist is warranted for:
  - abnormal NED screening lab results
  - borderline NED screening lab results in the individual with persistent symptoms in addition to a strong clinical suspicion
- If the patient continues to have normal NED screening labs and persistent symptoms, consider alternative diagnosis and referral
- Delay in diagnosis and treatment of NED may impair overall recovery and rehabilitation

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www.dcoe.health.mil ★ Outreach Center: 866-966-1020
February 2012

DEFENSE CENTERS OF EXCELLENCE
For Psychological Health & Traumatic Brain Injury

Mild Traumatic Brain Injury: Neuroendocrine Dysfunction

Indications and Conditions for Neuroendocrine Dysfunction Screening Post Mild Traumatic Brain Injury

Objectives

Upon completion of this educational module, the learner will be able to:

- Describe the basic pathophysiology of neuroendocrine dysfunction (NED) as it relates to mild traumatic brain injury (TBI), including the two primary endocrine glands that are affected during a blast injury
- Identify at least five symptoms that differentiate NED from persistent mild TBI symptoms
- Identify at least five laboratory tests used for NED screening post mild TBI
- Identify the major criteria for Endocrinology referral among patients with strong suspicion of NED

Scope of DCoE NED Recommendation

What it is:

The DCoE clinical recommendation described in this educational module is specifically intended for use in the mild TBI patient population, including:

- Individuals diagnosed with mild TBI with persistent symptoms at least three months post injury (post-concussion syndrome)
- Individuals who develop symptoms suggestive of neuroendocrine dysfunction up to 36 months post injury

This educational module is relevant to all health care professionals conducting screening for patients with mild TBI in any Defense Department (DoD) health care setting, including both primary and specialty care.

Scope of DCoE
NED Recommendation

What it is not:

The DCoE clinical recommendation described in this educational module is not intended for use for the moderate to severe TBI patient population, and patients with acute endocrine disorders, including adrenal crisis and hypoglycemic coma.

This educational module is not relevant to patients seen in an acute inpatient setting, and should not be used for screening other symptoms or disorders of the endocrine system.

Introduction

The information that follows on the definition, classification, and overall symptom profile of NED is provided:

- As introductory materials for those who are new to the subject of NED
- With an assumption that the reader has principal knowledge of TBI, including assessment, treatment and differentiation between mild, moderate and severe TBI

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Neuroendocrine Dysfunction (NED)

Background

Approximately 233,425 mild TBIs have occurred from year 2000 through Dec 2011 among service members

- 77 percent are classified as mild TBI
- The majority of mild TBI patients have symptoms that last only a short period of time, recovering within minutes to several weeks

Approximately 15 percent of patients (among civilian cohorts) with mild TBI experience persistent symptoms

- Of the approximate 15 percent who experience a mild TBI and remain symptomatic, an estimated 15-30 percent develop NED

Definition of NED

The term “neuroendocrine dysfunction” refers to a variety of conditions caused by imbalances in the body's hormone production directly related to the brain.

There are two areas of the brain responsible for regulating the production of hormones, the **hypothalamus** and the **pituitary gland.**

Damage to the hypothalamus or pituitary gland caused by TBI (including vascular damage, rupture, brain swelling, vasospasm, pituitary swelling or inflammation), may impact the production of pituitary hormones and other neuroendocrine functions of the brain.

TBI-Related NED

NED following TBI is the result of direct trauma (e.g., coup-contrecoup injury), or biochemical response to a blast exposure, that interferes with the normal production and regulation of hormones produced by the pituitary gland and the hypothalamus

Pathophysiology

The most common **hormonal deficiencies** associated with TBI include:

- Pituitary deficiencies (TSH/FSH/GH/IGF-1)
- Gonadotropin deficiencies (LH/FSH/testosterone/estradiol)

Adrenocorticotropic hormone, thyroid deficiency and prolactin deficiencies are also seen among patients with neuroendocrine involvement following TBI

List of Hormones

FSH	Follicle-Stimulating hormone
GH	Growth hormone
IGF 1	Insulin-like growth factor 1
LH	Luteinizing hormone
TSH	Thyroid-stimulating hormone

Hormone Deficiencies Symptoms

Growth hormone: Increased abdominal fat mass, fatigue, decreased vigor and concentration, decreased lean body mass, dyslipidemia, anxiety, depression, impaired judgment

Gonadotropin: Males — infertility, decreased libido, erectile dysfunction, decreased muscle mass, decreased exercise tolerance, anemia and testicular atrophy. Females — amenorrhea, sexual dysfunction, breast atrophy

Corticosteroid: Adrenal crisis, hypoglycemia, hyponatremia, myopathy, anemia, depression, fatigue, anxiety, apathy, weight loss, loss of libido

Hormone Deficiencies Symptoms

Thyroid hormone: Decreased energy, depression, cold intolerance, weight gain, fatigue, poor memory, muscle cramps, constipation, myopathy, hypotension, bradycardia, neuropathy, skin, hair and voice changes

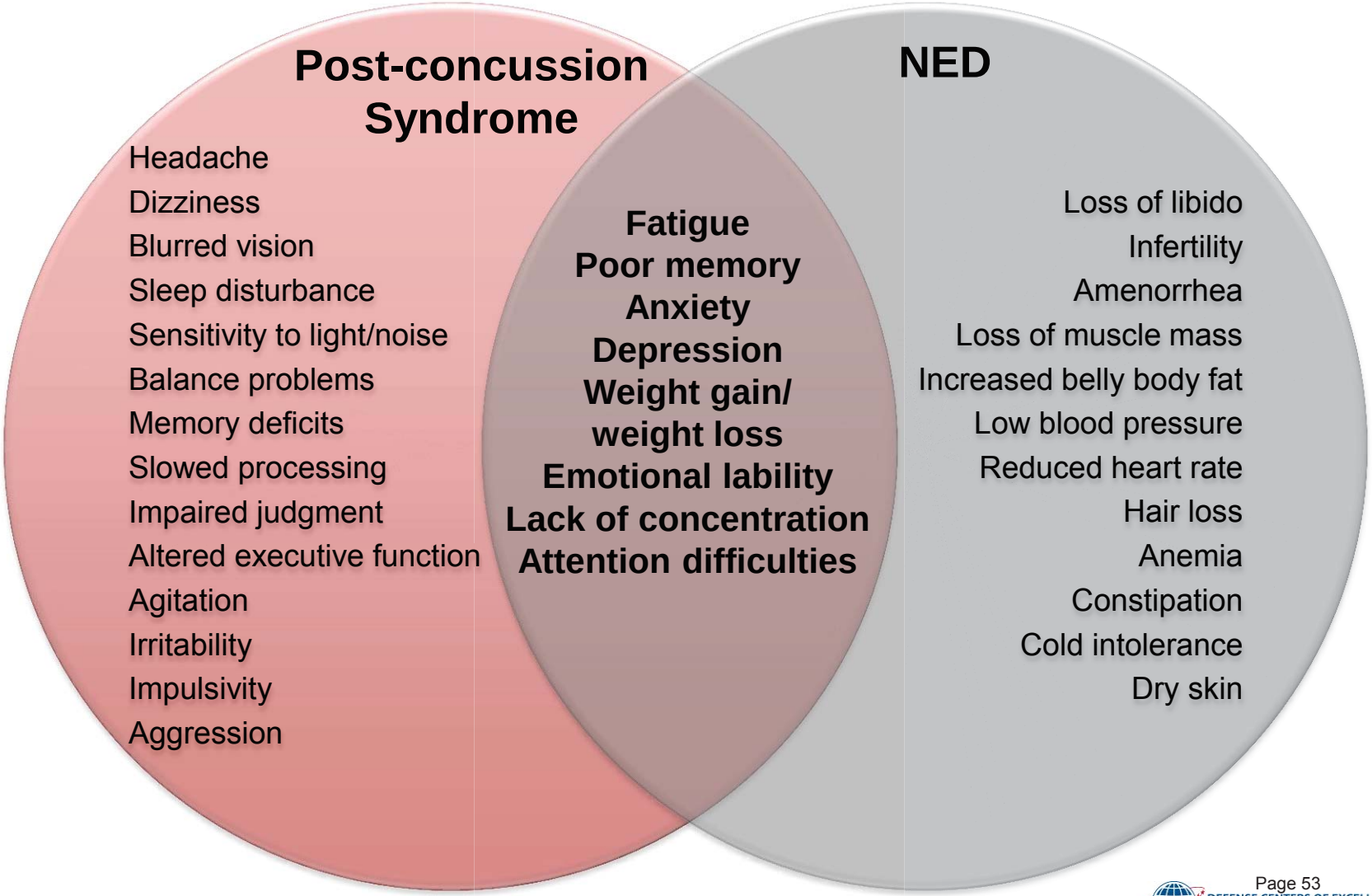
Prolactin: Males — decreased libido, impotence.
Females — amenorrhea, oligomenorrhea, galactorrhea, infertility, hot flashes, vaginal dryness, hirsutism (in post menopausal women).
Both — sudden onset of depression

Antidiuretic hormone: Excessive urination, dehydration, excessive thirst, hypernatremia (potentially leading to weakness, altered mental status, coma, seizures)

Hormone Deficiencies Symptoms

	Males & Females	Males	Females
Growth Hormone (GH)	Increased abdominal fat mass, fatigue, decreased vigor and concentration, decreased lean body mass, dyslipidemia, anxiety, depression, impaired judgment		
Gonadotropin (LH/FSH)		Infertility, decreased libido, erectile dysfunction, decreased muscle mass, decreased exercise tolerance, anemia, testicular atrophy	Amenorrhea, sexual dysfunction, breast atrophy
Corticosteroid (ACTH)	Adrenal crisis, hypoglycemia, hyponatremia, myopathy, anemia, depression, fatigue, anxiety, apathy, weight loss, loss of libido		
Thyroid-stimulating Hormone (TSH)	Decreased energy, depression, cold intolerance, weight gain, fatigue, poor memory, muscle cramps, constipation, myopathy, hypotension, bradycardia, neuropathy, skin, hair, and voice changes		
Prolactin (PRL)	Sudden onset of depression	Decreased libido, impotence	Amenorrhea, oligomenorrhea, galactorrhea, infertility, hot flashes, vaginal dryness, hirsutism (in post menopausal women)
Antidiuretic Hormone (ADH)	Excessive urination, dehydration, excessive thirst, hypernatremia (potentially leading to weakness, altered mental status, coma, seizures)		

Overlap of Symptoms



Symptoms Suggestive of NED

Behavioral, Emotional and Sleep Related Symptoms

- Depression
- Emotional lability
- Anxiety
- Fatigue
- Poor memory
- Lack of concentration

Symptoms Related to Reproductive Function

- Loss of libido
- Infertility
- Amenorrhea

Symptoms Suggestive of NED

Somatic Symptoms

- Loss of muscle mass
- Increased body fat around the waist
- Weight gain/weight loss
- Low blood pressure
- Reduced heart rate
- Hair loss
- Anemia
- Constipation
- Cold intolerance
- Dry skin

Screening for NED

NED should be considered in the differential diagnosis during screening for the following:

- Patients with persistent mild TBI symptoms suggestive of NED that do not resolve after **three months** from initial injury
- Patients with onset of **new** symptoms, suggestive of NED, up to **36 months** after the initial injury
- Patients with co-occurring conditions:
  - Review overlapping symptoms for NED and mild TBI, as well as other psychiatric disorders including sleep disorders, depression and posttraumatic stress disorder (PTSD). Symptoms include fatigue, poor memory, anxiety, depression, weight gain/weight loss, emotional lability, lack of concentration, attention difficulties

Delay in diagnosis and treatment of NED may impair overall recovery and rehabilitation of the mild TBI patient

NED Screening Recommendation

For patients with persistent symptoms suggestive of NED that do not resolve in **3 months** following mild TBI**,** OR patients with onset of new symptoms suggestive of NED up to **36 months** following mild TBI.

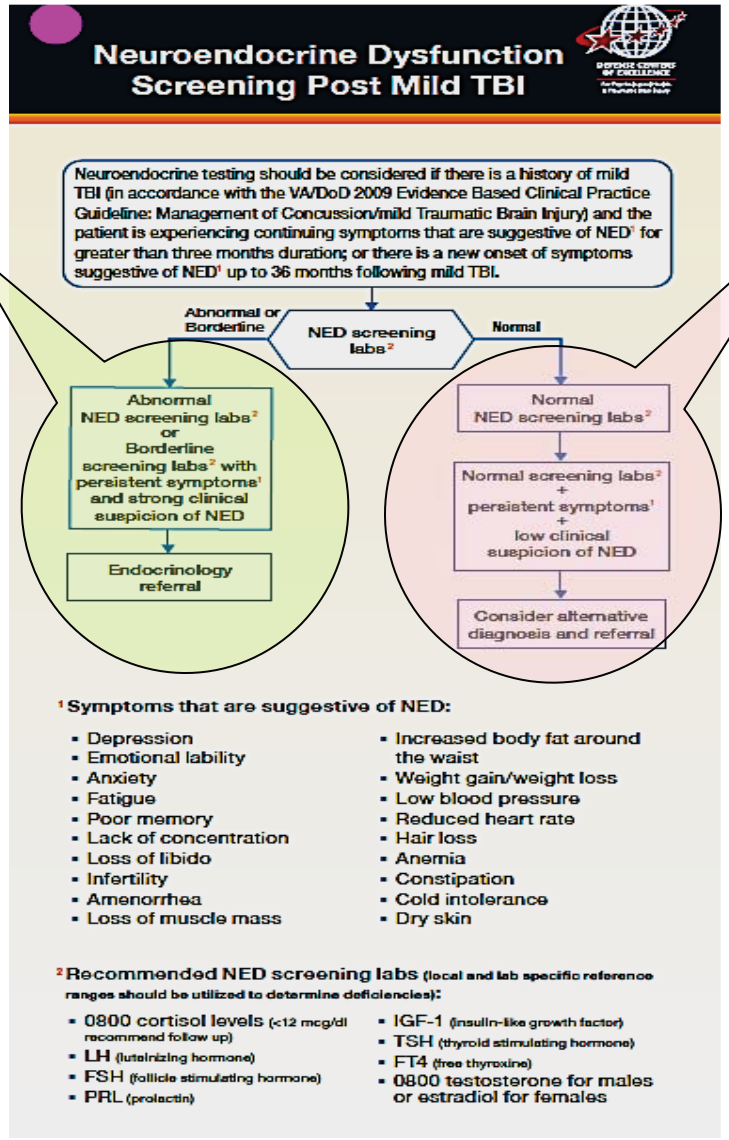
Recommended NED laboratory screening includes:

- 0800 Cortisol levels: <12 mcg/dl, recommend follow up
- Thyroid Stimulating Hormone
- Luteinizing Hormone
- Follicle Stimulating Hormone
- Prolactin
- Insulin-like Growth Factor
- Free Thyroxine
- Testosterone (males only)
- Estradiol (females only)

Clinical Recommendation

Consider referral to Endocrinology for:

- **Abnormal** NED screening lab results
- **Borderline** NED screening lab results among individuals with persistent symptoms and a strong clinical suspicion of NED



If the patient continues to have **normal NED** screening labs and persistent symptoms, consider alternative diagnosis and referral

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Case Study

NED Case Study

Air Force Staff Sgt. Cardenas is a medic who deployed twice to Afghanistan. He was involved in a mortar attack during his second tour. One of the mortars landed 10 feet from him. Cardenas does not remember losing consciousness, however complained of the following symptoms during his in-theater medical evaluation:

- Headache
- Sensitivity to light
- Dizziness
- Ringing of ears

NED Case Study *cont.*

Cardenas was evaluated, diagnosed and treated for mild TBI in-theater. His symptoms (sensitivity to light, dizziness and ringing of ears) resolved within 48 hours, except for a mild persistent headache.

Three weeks post injury, while still deployed, Cardenas developed the following symptoms:

- Anxiety
- Difficulty sleeping
- Lack of concentration
- Continues to have mild but transient headaches

He chooses not to seek medical attention assuming that symptoms are a result of deployment related stress.

NED Case Study *cont.*

Three months after his initial injury, Cardenas returns home from his deployment.

He continues to have difficulty concentrating at work and home. While his headaches have completely resolved, he continues to have difficulty sleeping, and increased anxiety. His symptoms are now weighing heavily on his personal life. He has a poor appetite but has gained 10 pounds since return from his deployment. He has also lost interest in sexual activity.

NED Case Study *cont.*

The primary care manager (PCM) at Cardenas' home base conducts further medical evaluation while considering the differential diagnosis including post-concussive syndrome, PTSD, depression and NED.

The PCM informs Cardenas that, although uncommon, mild TBI patients may experience neuroendocrine dysfunction three to 36 months after their initial injury, he orders the following labs:

- 0800 Cortisol levels: <12 mcg/dl, recommend follow up
- Thyroid Stimulating Hormone (TSH)
- Luteinizing Hormone (LH)
- Follicle Stimulating Hormone
- Prolactin
- Insulin-like Growth Factor
- Free Thyroxine
- Testosterone (males only)

NED Case Study *cont.*

Cardenas' results showed marginally low TSH, borderline testosterone deficiency and borderline low level of LH. However, all of the other lab results are normal.

Cardenas continues to experience persistent symptoms including:

- Low libido
- Loss of lean muscle mass
- Weight gain
- Anxiety
- Attention difficulties
- Mood disturbances

Cardenas' PCM recognizes a strong suspicion of NED based on unresolved symptoms and borderline lab results.

NED Case Study *cont.*

Test Question 1:

Identify possible symptom(s) that may overlap between NED and mild TBI.

a) Ringing in ears

b) Weight loss or weight gain

c) Lack of concentration

d) Answers b & c

e) All of the above

NED Case Study *cont.*

Test Question 2:

Due to possible delayed onset of NED, when should laboratory screening be considered for patients with persistent symptoms suggestive of NED?

a) 1-10 days from initial injury

b) 2-3 week from initial injury

c) 50 month from initial injury

d) 3-36 months from initial injury

NED Case Study *cont.*

Test Question 3:

Understanding the pathophysiology of NED, what glands are most likely affected in a patient presenting with symptoms of NED with history of TBI?

a) Hypothalamus

b) Adrenal glands

c) Pituitary gland

d) Answers a and c

e) All of the above

NED Case Study *cont.*

Test Question 4:

Based on Cardenas' symptoms, which of the following endocrine labs might be abnormal in an individual with mild TBI-related NED?

a) 0800 Cortisol

b) Luteinizing hormone

c) Prolactin

d) Testosterone

e) All of the above

NED Case Study *cont.*

Test Question 5:

Based on information presented in the case study, what should the PCM do next?

a) Endocrinology consultation

b) Consider alternative diagnoses and referral

c) Cognitive processing therapy

d) Prescribe selective serotonin reuptake inhibitor

e) All of the above

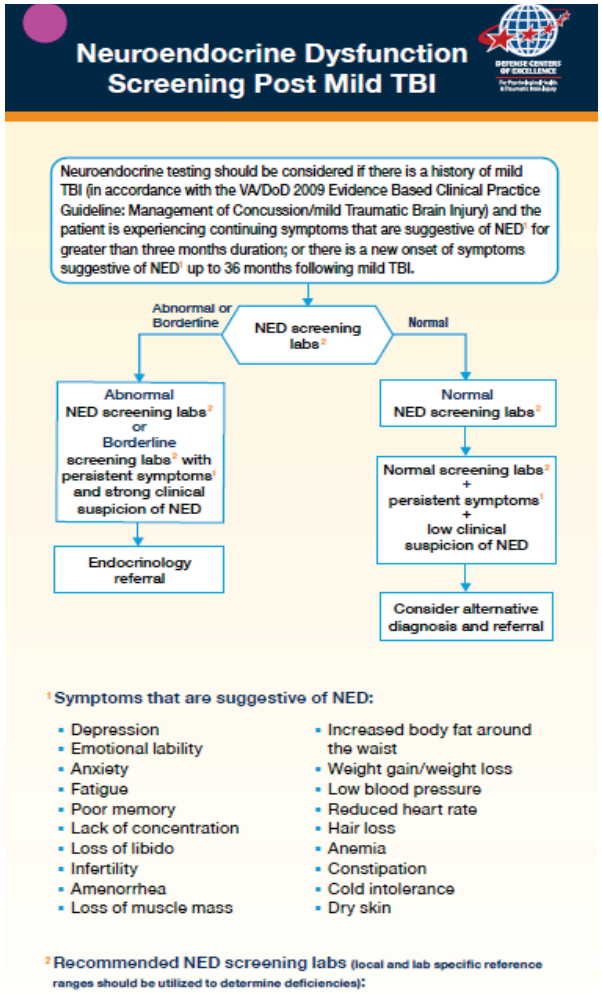
Resources

Defense Centers of Excellence for Psychological Health & Traumatic Brain Injury (DCoE)

dcoe.health.mil
Phone: 800-510-7897
Email: Resources@DCoEOutreach.org

Defense and Veterans Brain Injury Center (DVBIC)

www.dvbic.org
Phone: 866-966-1020
Email: info@dvbic.org



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Hypothesis and Objectives

The hypothesis of this study is that serum hormone deficiencies characteristic of hypogonadism and growth hormone deficiency (GHD) are significantly more frequent in US Marines who have sustained blast-related mild traumatic brain injury (mTBI), i.e., concussion, while deployed in Iraq, Operation Iraqi Freedom (OIF) or Afghanistan, Operation Enduring Freedom (OEF) (mTBI group) than in similarly deployed Marines not exposed to blast trauma (Non Blast Exposed (NBE) group). This hypothesis will be tested by measuring luteinizing hormone (LH), testosterone, and insulin-like growth factor-I (IGF-I) in predeployment and postdeployment serum samples from Marines in each of the two groups. The study will also investigate potential associations of hormonal abnormalities after blast mTBI with particular constellations of demographic, medical history, injury mechanism, and injury-specific data to determine to what extent each of these factors or combinations of factors best predict the occurrence of chronic pituitary dysfunction after blast concussion.

Background and Literature Review

Definition, impact, and prevalence of combat related mTBI/concussion OIF/OEF

The definition of mTBI/concussion [1] is a traumatically-induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by at least one of the following clinical signs immediately following the event: a loss of consciousness (LOC) of 0 to 30 minutes, alteration of consciousness/mental state for 24 hours or less, or post-traumatic amnesia for 24 hours or less. The terms “mTBI” and “concussion” are used interchangeably within the DoD [1].

Although termed “mild” in comparison to major brain injuries resulting in death, coma, or paralysis, mTBI, particularly repetitive mTBI, may have devastating personal, professional, and domestic consequences. Impairment of memory and concentration, increased anxiety, irritability and mood instability, fatigue, and sleep disturbance compromise combat performance and interfere with post-deployment job and family relationships, and can lead to substantial disability.

Concussion caused by blast effects of improvised explosive devices (IED) is the preeminent injury of deployment to Iraq or Afghanistan. The estimated prevalence of TBI in the 2.3 million American troops deployed to Iraq/Afghanistan from 2001 to 2011 is 20% [2]. A recent study found that in a sample of 2074 service members with TBI sustained in OIF combat, more than 95% were injured by blast mechanisms, and 91.7% of those were classified as mTBIs. 83.5% of the blast-related mTBIs were the result of IEDs. Another study of 4623 combat explosion episodes in Iraq found that the most frequent single injury type was mTBI [3]. These findings are similar to other studies from varying periods of OIF [4-7].

Rationale for studying hypopituitarism after blast

In investigations of civilian TBI from all causes, chronic pituitary dysfunction, or hypopituitarism, as defined by deficient production of one or more pituitary hormones measured at least one year after injury, has been reported to occur in 25–50% of cases [8,9]. By contrast, the prevalence of adult growth hormone deficiency in the general population has been estimated to be only approximately 300 cases per million, or 0.03% [10]. Despite the high incidence of blast

mTBI in combat in Iraq and Afghanistan and the high risk of hypopituitarism found in civilian studies of TBI, there had been no published investigations of diagnosis, frequency, or symptoms of hypopituitarism after blast mTBI prior to our recently published study. Furthermore, despite the universal and emphatic recommendations from studies of civilian TBI of the necessity of evaluating all victims for pituitary hormone deficits [8,9,11-18], screening of blast-exposed mTBI patients is not currently standard procedure. However, we found that 42% of Veterans with blast mTBI— but none of previously deployed Veterans without blast exposure— were found to have abnormal hormone concentrations consistent with pituitary dysfunction [11].

The anatomy of the pituitary makes it particularly vulnerable to rotational and linear forces generated during rapid acceleration/deceleration of the brain [19]. It is connected to the base of the brain by a narrow (2–3 mm) stalk that carries its vascular and neural supply that is highly vulnerable to disruption by brain movement and vascular pressure surges. The gland itself is almost completely encased in a pocket of the sphenoid bone, and because of this restriction it is subject to damage from compression resulting from brain movement or edema. Furthermore, the pituitary is located in the ventral-most portion of the brain (below the “helmet line”) that is particularly vulnerable to blast forces [12].

The most frequent hormonal deficiencies found after TBI, both in our published study and in civilian studies, are those indicative of growth hormone deficiency (GHD) or hypogonadism [13,14]. These two disorders are associated with numerous non-specific symptoms easily mistaken for behavioral symptoms of combat stress reaction or posttraumatic stress disorder (PTSD) including fatigue, mood disturbances, cognitive deficits, increased anxiety and depression, irritability, insomnia, sexual dysfunction, and decreased quality of life [15,16]. Both disorders are also associated with detrimental changes in body composition (increased fat, decreased muscle), increased frequency of cardiovascular disease, and increased mortality [17,18]. However, if accurately diagnosed as a consequence of hypopituitarism, these symptoms can in most cases be successfully relieved with hormone replacement.

Screening for hypogonadism is based primarily on measuring serum concentrations of LH and testosterone. LH is a gonadotropin secreted by the anterior pituitary that stimulates synthesis and secretion of testosterone by the testes. LH also has significant effects on spermatogenesis, fertility, and sexual behavior. A combination of low serum concentrations of both LH and testosterone is a strong indicator of hypogonadism.

There has been a substantial accumulation of evidence during the past twenty years confirming multiple deleterious consequences of adult GHD, and it has become recognized as a significant clinical problem. Single daytime measurements of circulating GH are unreliable diagnostic indicators of GHD because GH secretion is characterized by very low levels punctuated by large, widely spaced and unpredictable pulses. However, GH stimulates hepatic production of IGF-I, and markedly low concentrations of IGF-I are strong predictors of GHD. Therefore, daytime measurements of serum IGF-I provide a valuable screening tool.

Experimental Design

Population of interest

The subjects will be US Marines who have been deployed to Iraq or Afghanistan. The experimental group (mTBI) will be 75 Marines who have sustained a blast concussion as indicated by *International Classification of Diseases, Ninth Revision* (ICD-9) codes 850.0 (concussion with no LOC) and 850.1 (concussion with brief LOC)[20]. The control group (NBE) will be 50 Marines who have not sustained a blast-induced mTBI.

Inclusion/exclusion criteria

Inclusion criteria for both groups:

Service: Marines
Gender: male
Age: 18–40

Exclusion criteria for both groups:

History of head injury with loss of consciousness greater than 30 minutes
Penetrating head wound
Seizure disorder
Insulin-dependent diabetes
Current or past DSM-IV diagnoses of schizophrenia, other psychotic disorders, bipolar disorder, or dementia
DSM-IV diagnosis of alcohol or other substance abuse or dependence within 3 months prior to blood sampling

Inclusion criterion for mTBI group:

Single diagnosed blast concussion during deployment and at least one year prior to termination of deployment

Inclusion criterion for NBE group:

Absence of blast concussion or any documented head or face injury during period of deployment

Matching criteria

NBE and mTBI groups will be matched by age and categories of rank (E1–E3; E4–E5; E6–E9; WO/officer).

Requirements for serum sample selection

Eligible subject selection will be made using data in the Expeditionary Medical Encounter Database (EMED), formerly known as the Navy-Marine Corps Combat Trauma Register. The EMED is a collection of casualty clinical and tactical data sets from point of injury through rehabilitative outcome[21]. The EMED includes battle injury, nonbattle injury, disease, and sick-call encounters gathered from multiple DoD clinical and tactical databases.

A list of two hundred individuals meeting the inclusion/exclusion criteria for each subject group will be selected by the DoD-affiliated principal investigator, Michael Galarneau, MS, and co-investigator Mary Clouser, PhD, MPH, at the Naval Health Research Center (NHRC) in San Diego, CA and provided to the Armed Forces Health Surveillance Center Serum Repository. The

provided list will contain patient identifiers in order to assist the serum repository with the process of matching samples with the provided eligible population. We do not expect matched pre-post serum samples to be available for all 200 individuals on the selection list. Our goal is to obtain matched, de-identified 0.5 ml pre- and post-deployment serum samples from 125 individuals (75 mTBI, 50 NBE) meeting inclusion/exclusion criteria. Once the target number of samples meeting these criteria have been identified, no additional samples will be required. AFHSC will provide the de-identified samples, coded with randomly generated serum identification numbers to the non-DoD primary investigator, Charles Wilkinson, PhD, for measurement of LH, testosterone, and IGF-I by radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA).

AFHSC will provide a list of the serum identification numbers matched to the patient identifiers (originally provided by NHRC), will be sent to NHRC. The link between NHRC-provided SSNs and the AFHSC-provide serum identification numbers will allow for the demographic, medical history, injury mechanism and injury-specific data from the EMED database to be matched to the laboratory outcomes and determine to what extent each of these factors or combinations of factors best predict the occurrence of hypogonadism and/or GHD after blast concussion. The non-DoD primary investigator will never be provided any individually identifiable data by the DoD principal investigator. All identifiable information will remain at NHRC and stored according to DoD policy and the IRB protocol.

5) Statistical analysis

In order to establish normative data for each hormone, age-adjusted percentiles have been calculated based on the lognormal distribution from a reference control group of 100 subjects. From these percentiles, we will define hypogonadism (total testosterone less than the 5th percentile together with LH less than the 10th percentile) and GHD (age-adjusted IGF-I less than the 10th percentile). Differences between TBI and NBE groups in the pre- to postdeployment change in the proportion of subjects meeting the criteria for probable GHD will be tested using generalized linear mixed effects regression with GHD as the dependent variable, TBI group and deployment (pre vs. post) as independent fixed effects, and subject as a random effect, with the interaction between group and deployment being the primary effect of interest. Assuming the proportion of GHD in the control population to be 7%, and with sample sizes of 75 for the TBI and 50 for the NBE groups and a type I error of 5%, the minimum detectable difference in pre- vs. post-deployment change in the proportions of GHD between the NBE control group and the mTBI group achievable with 80% power with our study design is approximately 25%.

Differences in the proportion of post-deployment hypogonadism between TBI and NBE control groups will be tested using Fisher's exact test, as we expect no hypogonadism in pre-deployment subjects. Assuming the proportion of hypogonadism in the control populations to be 0%, and with sample sizes of 75 for the TBI and 50 for the NBE groups and a type I error of 5%, the minimum detectable difference in proportions of hypogonadism between the NBE control group and the mTBI group achievable with 80% power with our study design is approximately 16%.

Military relevance and benefit to the military/MHS population

For US service members in Iraq and Afghanistan, mTBI is the single most frequent injury from blast explosion. Studies of TBI from all causes in civilians have found a prevalence of pituitary dysfunction after brain injury of 25–50%. With the exception of our preliminary study, no investigations of the prevalence of chronic pituitary dysfunction after blast mTBI in service members or veterans have been published. Valid conclusions about the prevalence of pituitary dysfunction after blast mTBI cannot be made based on studies of civilian brain injuries because of the potential differences in injury mechanisms between impact trauma and blast trauma.

Blast forces result in more widespread and more multidimensional tissue damage than that resulting from impact. Blast waves are reflected from solid biological tissues resulting in shock waves of much greater intensity than the primary wave, and blast pressure is propagated from the body's periphery to the brain along primary blood vessels. A recent review by Cernak et al. states that the pathobiology of blast-induced neurotrauma (BINT) has characteristics not seen in other types of brain injury. "BINT represents a unique clinical entity caused by interwoven mechanisms of systemic, local, and cerebral responses to blast exposure" [22]. Investigations of civilian mTBI resulting from impact are unlikely to be appropriate for providing an understanding of the effects of blast concussion because of the different physical forces operating in the two conditions.

Therefore, investigations directed specifically at an understanding of the physics and pathophysiological consequences of blast mTBI and the most effective strategies for ameliorating and treating these injuries are of direct and significant relevance to the military/MHS population. Symptoms of pituitary dysfunction, particularly hypogonadism and GHD, comprise a constellation of non-specific behavioral, cognitive, and neuropsychiatric symptoms as well as deleterious changes in metabolism, body composition, physical activity and performance, sexual function, and quality of life. These potential consequences of blast-related hypopituitarism may have highly significant negative effects on the performance of military personnel under combat conditions and on recovery and rehabilitation after injury. If accurately diagnosed as a consequence of hypopituitarism, these symptoms can in most cases be treated quickly and successfully with hormone replacement. If the prevalence of pituitary dysfunction after blast concussion is as high as our preliminary data indicates, then the advisability of routine hormonal screening after blast mTBI becomes a highly significant consideration in maintaining military efficiency.

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